

Exhibit E

**UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON**

IN RE: ETHICON INC., PELVIC REPAIR
SYSTEM PRODUCTS LIABILITY
LITIGATION

MDL NO. 2327

THIS DOCUMENT RELATES TO:

WAVE 1 TVT Exact CASES

DEFENDANT ETHICON'S EXPERT REPORT OF TIMOTHY A. ULATOWSKI, M.S.

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I. Qualifications

I am a consultant on matters concerning medical device regulations, policies, and procedures administered by the Food and Drug Administration (FDA) and associated industry standards and practices. I am an independent consultant and maintain a registered business in the State of Virginia and the County of Fairfax, Virginia under the name Ulatowski Consulting, LLC.

I was awarded a Bachelor of Science degree in 1974 with a major in Microbiology from the Pennsylvania State University. In 1987 I was awarded a Master of Science degree in Physiology/Emphasis in Biomedical Engineering from the Georgetown University School of Medicine in a collaborative program with Catholic University Department of Engineering. I have additional college credits in computer science from the University of Maryland and Charles County Community College.

I was employed by the FDA from November 1974 until January 2011. During my 36 plus years of employment with FDA I held increasingly responsible positions, first for 7 years in what is now known as the Center for Drug Evaluation and Research (CDER), and the remaining years in the Center for Devices and Radiological Health (CDRH). CDRH is responsible for evaluation and clearance or approval of new medical devices, evaluation of medical device clinical investigations, ensuring compliance with medical device laws and regulations administered by the FDA, postmarket vigilance of marketed devices, and research on emerging device technologies.

From 1974 until 1978 I held the position of Microbiologist in the National Center for Antibiotic Analysis where I conducted laboratory analyses on antibiotics for regulatory certification purposes. From 1978 until 1980 I held the position of Consumer Safety Officer (CSO) in the Office of New Drug Evaluation (ONDE). While in ONDE I was a product manager for the Anti-inflammatory Drugs Group and I also contributed to the Oncology and Radiopharmaceutical Drugs Groups. I was the Executive Secretary for the Arthritis Advisory Committee and managed the flow of work and outputs concerning investigational new drug applications (INDs) and New Drug Applications (NDAs). I also was the division lead on major issues such as the Drug Efficacy Study Implementation (DESI) program and the Radiopharmaceutical Drug Research Committee program. In this capacity I became expert in FDA drug regulations, policies, and procedures.

In 1980 I joined the Office of New Device Evaluation (NDE), Program Management Group, in the Bureau of Medical Devices (BMD) as a CSO. BMD was soon reorganized and joined with the Bureau of Radiological Health to form CDRH. NDE was renamed the Office of Device Evaluation (ODE).

I was assigned to the Investigational Device Staff and was responsible for formulating policies and procedures to implement the newly effective investigational device exemptions regulation, 21 CFR Part 812, and other new human subject protection regulations, 21 CFR Parts 50 and 56. I evaluated investigational device exemption applications (IDEs) including protocols for clinical studies. I also evaluated and quality controlled the IDE review work of all the divisions in ODE.

In 1988 I was promoted to the Director of the IDE Staff. In that capacity I was responsible for managing and directing the IDE staff, for making final decisions on the sufficiency of IDE applications and the review of those submissions by FDA staff, and for IDE regulatory compliance in collaboration with the Office of Compliance, CDRH. In this position I became thoroughly knowledgeable about IDE regulations, policies and procedures, clinical studies and when those studies may be needed to substantiate the safety and effectiveness of devices, as well as associated industry standards and practices.

Later in 1988 I transferred to the position of Branch Chief, General Hospital Devices in ODE. My position classification changed to Supervisory Biomedical Engineer. As Branch Chief I managed and directed the branch staff, and was a primary reviewer of IDE applications, Premarket Notification Submissions (510(k)s), Premarket Approval Applications, new product labeling, medical device reports (MDRs) and other types of regulatory submissions under the purview of my branch. My branch evaluated products classified by FDA under 21 CFR Part 880, General Hospital Devices. The products in this classification regulation include, for example, infusion pumps and ports, administration sets and intravascular catheters. In this position I became thoroughly knowledgeable about premarket submission and medical device reporting regulations, policies and procedures, as well as associated industry standards and practices.

In 1991 I was promoted to the position of Associate Director for General Devices in ODE. The scope of my responsibilities expanded to include the premarket evaluation of surgical devices classified under 21 CFR Part 878 as well as the previously assigned general hospital products. In this capacity I had broader influence on guidance, policy and procedure development spanning the entire ODE. I formulated guidance, policies and took numerous premarket actions on many significant new products such as medical lasers and computerized medical systems.

In 1996 I was promoted to the Director, Division of Dental, Infection Control and General Hospital Devices in ODE. In this position I assumed responsibility for more product areas and all the premarket regulatory activities associated with those product areas. During the course of my tenure as Division Director, I assumed responsibility for even more types of devices such as anesthesiology devices.

During my tenure at FDA I participated as a member on national and international standards committees and the Global Harmonization Task Force (GHTF). I was the co-chair of the committee that created the existing standards program in CDRH. The CDRH standards program evaluates national and international standards to determine if FDA should recognize and utilize them as means to support product development and premarket submissions. The GHTF created internationally harmonized medical device regulatory guidance documents now used around the globe. During this time I also wrote the first FDA guidance documents on infusion pumps and accessories, infusion ports, sterilizers, chemical germicides, and guidance on labeling of devices intended for reuse.

In 2003 I was promoted to Director, Office of Compliance, CDRH. As the office director I supervised a large staff that was responsible for ensuring compliance with the medical device, radiological health, and human subject protection laws and regulations administered by FDA. I

had many duties including, for example: managing inspections of manufacturing facilities and clinical investigation sites; evaluating Quality System(QS), MDR, and recall-related inspection reports; evaluating and directing advisory or enforcement actions; classifying recall actions; creating FDA risk management strategies; evaluating advertising, labeling and promotional literature; directing actions on violations of the medical device reporting regulation; leading the FDA Device Field Committee, which is composed of chief inspectors and senior compliance officers, and; managing responses to violations of import/export and registration laws and rules. In this position I became thoroughly knowledgeable about FDA law and regulations concerning medical devices and associated industry standards and practices.

I transitioned to the position of Senior Advisor for Enforcement in October 2010 in anticipation of my retirement and to allow an orderly succession of leadership. During the last four months of my FDA career I led a team formulating strategies in advance of Congressional user fee reauthorization and I provided expert advice to senior FDA leadership on premarket and compliance programs. The Commissioner awarded me for my work on user fee legislation.

During my employment with FDA I received virtually every type of award FDA can bestow including the Distinguished Career Service Award, Award of Merit, Commendable Service Awards, and numerous other individual and group awards. I maintained my management and regulatory expertise during the course of my career by attending numerous professional meetings, courses and seminars. I was frequently an invited speaker or major participant at regulatory and professional conferences here and abroad such as those held by the Food and Drug Law Institute, Regulatory Affairs Professional Society, and the American Medical Association. I remain current on FDA matters.

I now am an independent consultant working on medical device regulatory issues such as premarket submissions, postmarket surveillance, promotion and advertising, and quality systems. I advise medical device and drug manufacturers on premarket and compliance issues, and provide expert testimony on FDA-related regulatory matters in litigations. I continue to be an invited speaker at professional and industry meetings. At the request of the US government I trained international regulators on medical device premarket and postmarket programs in 2013 and 2014.

A copy of my curriculum vitae is attached as Appendix A.

I am being compensated in this litigation through NDA Partners LLC. The rate they charge for my services to Butler Snow is \$500/hr.

II. FDA's Mission, Statutory and Regulatory Provisions Relevant to the Subject Case

FDA is a consumer protection agency that has roots stretching back to the turn of the last century. Its statutory authority is derived from the Federal Food, Drug, and Cosmetic Act (the act) (21 USC 301 et seq.)¹ and other acts that have been amended from time to time. Regulations

¹ References to the act are stated according to United States Code.

implementing the statutory provisions are published in Title 21, Code of Federal Regulations (21 CFR). The medical device amendments to the act were enacted on May 28, 1976.

FDA regulates medical devices. Tension Free Vaginal Tape (TVT) is a medical device. A medical device is defined under 21 USC §321(h) as:

“an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals, or (3) intended to affect the structure or function of the body in man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependant upon being metabolized for the achievement of its primary intended purposes.”

FDA regulates the entire life cycle of medical devices. For example, FDA evaluates investigational studies for new products before the studies commence², it inspects manufacturing facilities³, it evaluates marketing applications, and it monitors device safety and effectiveness during the entire course of their use. FDA regulations govern each of these activities and FDA makes available related guidance documents to be used by industry, FDA staff and the public.

A. FDA’s Medical Device Program

CDRH is the primary organization within FDA that regulates medical devices. Other FDA Centers also have authority to regulate medical devices using device law and regulations. Combination products are therapeutic or diagnostic products that consist of more than one regulated article, e.g., drug/device, biological/device. Each combination product is regulated by one primary Center.

CDRH has over 1000 employees and is organized into offices. For example, ODE is responsible for review of new products, except for in-vitro diagnostics and radiologic products, the Office of Compliance (OC) is responsible for compliance and enforcement activities and the Office of Surveillance and Biometrics (OSB) is responsible for evaluating postmarket surveillance reports, epidemiology and statistical reviews. Information from each office within CDRH is integrated in computer systems available for all employees to access and use in the course of performing their jobs. For example, a compliance officer in the Office of Compliance can easily access postmarket reports, inspection records, and premarket records for specific companies. CDRH leverages the considerable manpower in the

² FDA does not approve “non-significant risk” devices before studies commence. This evaluation and approval is delegated to institutional review boards (21 CFR Part 56).

³ FDA has authority to inspect all facilities subject to inspection, e.g., all places related to quality system and medical device reporting activities (21 USC §374).

Office of the Associate Commissioner for Regulatory Affairs in order to conduct inspections, and it uses special government employees and third parties for premarket review activities.

CDRH obtains information on medical devices for review and analysis by many means. For example, it receives required submissions according to procedures in regulations, it proactively collects information and evidence during inspections, it uses public sources of information, and increasingly it relies on regulatory bodies in other countries to provide information to it on regulated products. FDA has extensive test facilities and conducts laboratory and engineering analyses on regulated products for compliance, premarket and postmarket surveillance purposes. Manufacturers generate the data and information in premarket submissions.

B. Prohibited Acts, Misbranding and Adulteration and FDA Enforcement of Laws and Regulations It Administers

The F,D &C Act prohibits specific acts or the causing thereof. Two relevant prohibitions to this litigation under are adulteration and misbranding.⁴ The act prohibits the following, in part:

Introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded;

Adulteration or misbranding of any food, drug, device, or cosmetic in interstate commerce; and

Receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

1. Adulteration

The act deems a device to be adulterated, in part (paraphrased):⁵

If it is a device and the methods used in, or the facilities or controls used for, its manufacture, packing, storage, or installation are not in conformity with applicable good manufacturing practices.

2. Misbranding

The act deems a device to be misbranded, in part (paraphrased):⁶

If its labeling is false or misleading in any particular;

Unless its labeling bears (1) adequate directions for use; and
(2) such adequate warnings against use in those pathological

⁴ 21 USC §331.

⁵ 21 USC §351(h).

⁶ 21 USC §352.

conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement;

It is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended, or suggested in labeling thereof;

If a notice or other information respecting it was not provided as required by such section or section 510(k); or

For which there has been a failure or refusal to give required notification or to furnish required material or information such as section 519, medical device reports.

The act also provides the following regarding misbranding:⁷

"If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual."

The misbranding provisions of 21 USC §§352(q) and (r) relating to advertising for devices do NOT apply to TVT devices because TVT devices are not restricted devices.⁸

3. Enforcement of the Laws and Regulations Administered by FDA

The FDA Regulatory Procedures Manual (RPM)⁹ directs FDA personnel on internal procedures to be used in processing domestic and import regulatory and enforcement matters. While the RPM is intended mainly to provide guidance to FDA inspectors, investigators, and compliance officers, the document is useful to all of FDA and informative to the device industry.

⁷ 21 USC §321(n).

⁸ Devices must be designated by FDA as "restricted," either by a regulation promulgated under 21 USC §360j(e)), or by a premarket approval application (PMA) approval order pursuant to 21 USC §360e(d)(1)(B)(ii)). Neither applies to TVT devices.

⁹ FDA Regulatory Procedures Manual, <http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176446.htm>.

The RPM describes the actions FDA may take to ensure compliance with the laws and regulations it administers. Those actions include advisory, administrative, judicial and import actions, and recall, emergency and other procedures. The key offices responsible for these medical device actions and procedures include the Office of Compliance/CDRH, the staff of the Associate Commissioner for Regulatory Affairs, and the FDA Chief Counsel's office. Other offices contribute only as needed.

According to the RPM, "When it is consistent with the public protection responsibilities of FDA and depending on the nature of the violation, it is FDA's practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. **Warning and Untitled Letters**, both advisory actions, are issued to achieve voluntary compliance and to establish prior notice. The use of these letters and the prior notice policy are based on the expectation that most individuals and firms will voluntarily comply with the law."

The FDA compliance offices may exercise enforcement discretion when deciding whether to take enforcement action. Also, the RPM notes "there are instances when issuing a Warning Letter is not appropriate, and, as previously stated, a Warning Letter is not a prerequisite to taking enforcement action. Examples of situations where the agency will take enforcement action without necessarily issuing a Warning Letter include:

1. The violation reflects a history of repeated or continual conduct of a similar or substantially similar nature during which time the individual and/or firm has been notified of a similar or substantially similar violation;
2. The violation is intentional or flagrant;
3. The violation presents a reasonable possibility of injury or death;
4. The violations, under Title 18 U.S.C. 1001, are intentional and willful acts that once having occurred cannot be retracted. Also, such a felony violation does not require prior notice. Therefore, Title 18 U.S.C. 1001 violations are not suitable for inclusion in Warning Letters; and,
5. When adequate notice has been given by other means and the violations have not been corrected, or are continuing."

Relevant administrative actions include Section 305 notices (Citations), Section 305 meetings, administrative detention of devices, and civil money penalties (CMPs). **Detention and civil money penalties** are the most common actions taken. FDA may detain devices for a period of up to 30 calendar days if, during an inspection, the FDA has reason to believe the devices are adulterated or misbranded. The intent of administrative detention is to protect the public by preventing distribution or use of violative devices until FDA has had time to consider the appropriate action to take and, where appropriate, to initiate a regulatory action. The action of choice, in most cases, is a seizure. CMPs are monetary penalties that are assessed by FDA for violations of the law and regulations.

Some relevant judicial actions include seizure, injunction and prosecution. For a **seizure**, the United States of America, as plaintiff,

proceeds under the Supplemental Rules for Certain Admiralty and Maritime Claims (Supplemental Rules) by filing a Complaint for Forfeiture and obtaining a warrant for arrest of the device, directing the United States Marshal to seize (take possession or place in constructive custody of the court) the device. An **injunction** is a civil judicial process initiated to stop or prevent violation of the law, such as to halt the flow of violative products in interstate commerce, and to correct the conditions that caused the violation to occur. FDA can refer cases to the Department of Justice for **criminal prosecution**.

As part of import operations the government may **refuse to admit** devices for import and can **detain** devices upon import. Section 801(a) of the Federal Food, Drug, and Cosmetic Act directs the Secretary of the Treasury to issue a Notice of Refusal when it appears from examination of samples, or otherwise, that an imported shipment is in violation. This Section also orders the destruction of any such shipment refused admission, unless it is exported within 90 days of the date of the notice, or within such additional time as may be permitted pursuant to such regulations. FDA may refuse to admit devices based on information, *other than the results of examination of samples* that causes an article to appear to violate the Act.

Two common additional procedures are the **regulatory meeting** and "**It has come to our attention**" letters. A Regulatory Meeting is a meeting requested by FDA management, at its discretion, to inform responsible individuals or firms about how one or more products, practices, processes, or other activities are considered to be in violation of the law. FDA is not required to hold a Regulatory Meeting and, except for a few specifically defined areas, is not required to provide any other form of notice before taking an enforcement action. An "It has come to our attention letter" may be issued by the Office of Compliance where a potential violation has been observed and FDA requests information to assess the activity. It is not an advisory or enforcement letter.

Advisory, enforcement or other compliance actions are generally initiated by the Office of Compliance¹⁰ or the Associate Commissioner for Regulatory Affairs's office based upon potential violations identified by many sources, e.g., inspections, public or industry complaints, FDA surveillance of public information, or internal agency referrals. Only compliance and enforcement staff with the delegated responsibility can initiate, process or issue an enforcement or advisory action.

The Office of Compliance assesses internal agency referrals of a potential violation, e.g., a referral from the Office of Device Evaluation. The Office of Compliance's initial assessment includes, for example, a determination if the referral describes an activity that may be a violation, whether there is adequate documentation of the activity, and an analysis of the risk to the public health.

¹⁰ The Office of In-Vitro Diagnostic Devices and the Office of Surveillance and Biometrics can initiate compliance actions but the actions must be processed and approved through the Director of Compliance.

4. Regulations Concerning Designing and Testing Medical Devices Prior to Marketing

The development and marketing of a medical device has been characterized as a life cycle. The cycle begins with a concept for a new or modified device, proceeds through design phases, the design is transferred to manufacturing and the device is placed on the market. The cycle is complete when the device becomes obsolete or is modified.

The Design Controls provisions of the FDA Quality System regulation, 21 CFR §820, provide the requirements a manufacturer must incorporate into its design and development procedures and processes. Design controls consist of requirements for (1) design and development planning, (2) identifying all appropriate design inputs, (3) defining design outputs, (4) ensuring that design reviews are conducted at periodic intervals, (5) verifying that design outputs meet design inputs requirements, (6) validating that the finished device meets user needs, and (7) transfer of the design to manufacturing. Documentation of design activities is captured in the Design History File. Design changes are a managed process with the need for such actions as review and approval of changes, verifications and revalidation of the design, when needed, before implementing the changes.

FDA recognizes that manufacturers are constantly developing new and improved devices and bringing these devices to the market even while prior versions of the same type of device continue to be legally marketed. The prior devices often remain on the market until the manufacturer decides to discontinue the previously marketed devices for marketing reasons.

There is no requirement to tell FDA in a PMA or 510(k) about next generation devices in the development pipeline. Manufacturers' design and quality data concerning devices being developed are subject to FDA inspection.

Risk management is the systematic application of management policies, procedures, and practices to the tasks of identifying, analyzing, controlling, and monitoring risk.¹¹ Risk management is intended to be a framework within which experience, insight, and judgment are applied to successfully manage risk. Risk analysis, part of risk management, is required by the quality system regulation. Risk management as a whole process, while not a requirement of the quality system regulation, is addressed in quality system guidance because of its importance on all aspects of the life cycle of a device.

Risk management begins with the initial development of the design input requirements and assessment of risks known or anticipated at the initial stages of product design. In this way, unacceptable risks can be identified and managed earlier in the design process when changes are easier to make and less costly. Failure Modes and Effects Analyses (FMEAs), Risk Management Reports, and Device Design Safety Analyses

¹¹ See discussion of risk management in FDA Design Control Guidance, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070627.htm>. The International Standards Organization (ISO) Standard 14971:2007 is commonly utilized to develop the processes and procedures associated with risk management activities.

(DDSAs) are examples of commonly used tools in the design and risk management processes.

Risks management is an iterative process. As new information becomes available about risk the manufacturer should assess this information and take action as appropriate and practicable to mitigate the risk.

Probability estimation and determination of a probability score is a part of risk analysis. ISO 14971:2007 states:¹²

"Seven approaches are commonly employed to estimate probabilities:

- Use of relevant historical data
- Prediction of probabilities using analytical or simulation techniques
- Use of experimental data
- Reliability estimates
- Production data
- Post-production information
- Use of expert judgment"

Severity is also a risk analysis factor. The manufacturer determines how many levels of severity there are for a particular risk assessment and how the levels are defined.¹³ Each level has an associated score.

Risk acceptability is typically displayed on a severity versus probability table with acceptable, unacceptable and as low as reasonably possible regions defined by the manufacturer. All risks should be reduced to the lowest level practicable based on technical and economic factors.

Manufacturers often use risk priority numbers (RPN) in their analyses. The RPN is a value determined by multiplying scores of severity by occurrence by detection. Risk reduction actions affect the RPN by lowering the RPN. Manufacturers often have cut-off values for RPNs to define highest priority risks to address.

If a risk is not acceptable, as determined by the manufacturer, after risk reduction measures have been applied then a risk/benefit analysis determines if the benefit outweighs the residual risk. The ISO standard provides that the risk/benefit decision is made by "experienced and knowledgeable individuals."¹⁴ These individuals may be, for example, medical staff.

5. Regulations Concerning Paths to the Market; Premarket Notification Submissions (510(k)s)

a. Paths to the Market

There are two main regulatory paths to the market for medical devices. One path is FDA approval of a premarket approval application and the other is by FDA clearance of a premarket notification submission,

¹² ISO 14971:2007, Section D.3.2.2; Manufacturers sometimes use the probability cut points described in the standard when devising their risk procedures.

¹³ ISO 14971:2007, Section D.3.3.

¹⁴ ISO 14971:2007, Section D.6.1.

commonly known as a 510(k) submission. The path most appropriate for a device depends primarily on its FDA regulatory classification. For purposes of this report on the Ethicon TVT devices, I will concentrate on the 510(k) submission pathway to classification and clearance for marketing.

The act establishes three classes of devices, Class I, II, and III.¹⁵ The act provides regulatory controls for each class to provide reasonable assurance of safety and effectiveness for devices within the class. Class I is subject to "General Controls" including, for example, adulteration and misbranding, registration and listing, adverse event reporting, and good manufacturing practice (quality system requirements). In addition to General Controls, Class II devices are subject to "Special Controls" that may include, for example, specific guidance and patient registries. Class III devices are subject to Premarket Approval but also must meet General Controls.

FDA, based on the recommendations of panels of experts, classified all devices on the market on May 28, 1976 into one of the three classes based upon their assessment of safety and effectiveness of those devices. The devices were grouped into generic types. The classification for each type of device is in 21 CFR, Parts 862-892.

For specific devices not on the market on May 28, 1976 the act provides that any device intended for human use which was not introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976 is classified in class III unless the device is substantially equivalent to a type of device (a predicate device) classified into class I or II. FDA determines whether the new device is substantially equivalent to a predicate by means of what the act describes as a "report" submitted to FDA preceding introduction of the device into interstate commerce.

The act describes the form and manner of the "report".¹⁶ It provides, in part, that each person who is required to register and who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device intended for human use shall, at least ninety days before making such introduction or delivery, "report" to FDA (in such form and manner as FDA shall by regulation prescribe) (1) the class in which the device is classified under Section 360c or if such person determines that the device is not classified under such section, a statement of that determination and the basis for such person's determination that the device is or is not so classified, and (2) action taken by such person to comply with requirements under 21 USC §360d (standards) or Section 360e (premarket approval) which are applicable to the device. These original fundamental provisions of a 510(k) "report" have been expanded, defined, and enriched in several amendments to the act after 1976.

The term "substantially equivalent", which I have noted above, is at the core of classification by means of a 510(k) submission. An amendment to the act in 360c(i) incorporated a definition of the term that FDA had previously included in guidance. According to the act, substantial equivalency means that the new device has the same intended use as the predicate device and the same technological characteristics,

¹⁵ 21 U.S.C. §360c.

¹⁶ 21 U.S.C. §360(k).

or if it does not have the same characteristics then information submitted demonstrates that the new device is as safe and effective as the predicate and does not raise different questions of safety and effectiveness than the predicate device. The FDA review criteria for a 510(k) incorporate this statutory provision and expands upon it.

b. Premarket Notification Submissions

The 510(k) regulation, 21 CFR §807.81, describes when a 510(k) is required. In part, a 510(k) is required for a device being marketed for the first time or for a marketed device that is to be significantly changed or modified in design, components, method of manufacture, or intended use.

The regulation under 21 CFR §807.87 also describes information required in a 510(k). The 510(k) must include, in part: labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use; comparisons to other legally marketed devices, and; any other information FDA needs to determine substantial equivalence.¹⁷ FDA's review of 510(k) data and information for implants is rigorous and thorough.

There is FDA guidance pertaining to 510(k)s. Some FDA guidance applies to the submission process in general¹⁸ while product-specific guidance, if available, provides more details on format and content for a 510(k) or PMA, such as standards that should be applied, tests and results and specific labeling recommendations. Good Guidance Practices (GGPs) state "You (for instance a manufacturer) may choose to use an approach other than the one set forth in a guidance document. However, your alternative approach must comply with the relevant statutes and regulations."¹⁹ GGPs also state "Although guidance documents do not legally bind FDA, they represent the agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence."

FDA issued guidance for surgical mesh, which is the generic type of device under which TVTs are included.²⁰ The guidance recommends that 510(k)s for surgical mesh include, in part: a summary of safety and effectiveness or a statement that such information is available upon request, specification of all material components of the device, manufacturing information, packaging information, product characterization, and labeling. The document states a final consideration that additional information may be required as technological advances continue but it does not specifically identify the need for clinical data.

¹⁷ "any other information" may include, for example, preclinical or clinical data, or revised labeling.

¹⁸ 510(k) Submission Process,

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm070201.htm>.

¹⁹ 21 CFR §10.115.

²⁰ Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance - Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073790.htm>.

There are three types of 510(k) submissions including traditional, special and abbreviated. Traditional submissions can be used under any circumstances and include all information typically required for a 510(k). Abbreviated submissions may include less information than a traditional submission because this submission method relies on "declarations of conformity" to FDA-recognized standards used in support of the design and manufacturing of the type of device. These declarations reduce the amount of standards-related data submitted. A special 510(k) may be used when a manufacturer wishes to significantly modify a legally marketed device. The latter two processes are described in FDA guidance.²¹

FDA may determine, by order, a 510(k) submission to be substantially equivalent (SE), SE with limitations,²² not substantially equivalent (NSE), or provide a letter that additional information is needed to render a decision (AI). FDA considers a device that is found SE by means of a 510(k) to be "cleared." A device is "approved" only by an approval decision rendered by FDA for a premarket approval application.

Prior to the Safe Medical Devices Act of 1990 (SMDA)²³ manufacturers could go to market after 90 days of submission of the 510(k) unless FDA intervened beforehand with either a call to the submitter to "hold" the review clock, or by an Additional Information (AI) or Not Substantially Equivalent (NSE) letter. The current language in the standard AI letters that "You may not market this device until...you have received a letter from FDA allowing you to do so" was included in the form AI letter after SMDA in 1990 because after SMDA an FDA order was needed allowing the marketing of the device. There is only one format for AI letters even though, in my experience, the above stipulations of the letter are not enforced in certain cases.²⁴ The AI letter is also an administrative letter issued by ODE, i.e., it is not a compliance action.

FDA notes that there are "...many changes in the evolution of a device."²⁵ A manufacturer determines that a new 510(k) is needed according to regulation when:

²¹ The New 510(k) Paradigm:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm>.

²² Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff (Update to 98-1), <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082162.htm>.

²³ SMDA, The Safe Medical Devices Act of 1990 (P.L. 101-629), which amended the FFD&C Act (21 U.S.C. 201 et seq.), was signed into law on November 28, 1990.

²⁴ Two cases of enforcement discretion include (1) changes to a device submitted in a 510(k) after a recall. (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080297.htm>), and (2) submission of a 510(k) after FDA requests voluntary submission and ODE makes a referral to OC, e.g., a prior change to a marketed device is deemed significant by FDA.

²⁵ FDA Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device.

"the device is one that the person currently has in commercial distribution or is reintroducing into commercial distribution, but that is about to be significantly changed or modified in design, components, method of manufacture, or intended use. The following constitute significant changes or modifications that require a premarket notification:

- (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.
- (ii) A major change or modification in the intended use of the device."²⁶

The FDA guidance document "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997"²⁷ was developed to help assist manufacturers in deciding when a change to a device was "significant" or "major." FDA notes in the guidance "To be certain that a decision on when to submit a 510(k) is correct, one would probably need to enumerate all device types and all potential types of changes and then match each combination of device and change with a decision. Given that there are thousands of individual device types and possibly tens or hundreds of enumerable changes, this would be an impossible task. Furthermore, the resultant guidance would fill volumes, would probably be difficult to use, and would be unlikely to keep pace with an ever-changing technology."

While the guidance tries to provide general guidance on making decisions regarding changes to devices it is clear that FDA relies heavily on manufacturer compliance with the Quality System (QS) regulation as the fundamental means of ensuring device safety and effectiveness. The guidance states, "For many types of changes to a device, it may be found that a 510(k) is not necessary, and the Agency may reasonably rely on good manufacturing practices (either as implemented under the 1978 GMP or the Quality Systems regulation) to continue to assure the safety and effectiveness of the changed device. This reliance is enhanced when manufacturers document their decision-making based on their testing results or other design validation criteria." Also, manufacturers "must have a process in place to demonstrate that the manufactured device meets the change in design specifications (or the original specifications, if no change was intended). They must keep records, and these records must be made available to an FDA inspector." The guidance states, "No matter how carefully this guidance is applied, there will still be decisions in a "gray area" that manufacturers will have to make (emphasis added)."²⁸ Manufacturers are encouraged, but not required (emphasis added), to contact FDA when the proposed change is not addressed in the guidance flowcharts. In fact, in my experience it was rare that a manufacturer called my division in ODE to request an opinion on a change to a marketed device.

²⁶ 21 CFR §807.81(3).

²⁷ FDA Guidance, Deciding When to Submit a 510(k), <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Guidancedocuments/ucm080235.htm>.

²⁸ Ibid.

It was reported in 2008 that there are more than 20,000 companies worldwide and 80,000 brands and models of devices.²⁹ So, based on the fact that FDA notes there are numerous changes with devices, there are probably tens of thousands of changes in any given year. However, there were only 3363 510(k)s submitted in 2008, and only 653 were special 510(k)s.³⁰ Various conclusions could be drawn from these data but it is evident that relatively few changes to marketed devices result in new 510(k) submissions.

FDA proposed a revision to the K97-1 guidance in 2011 based upon its current thinking about changes to devices. Congress rebuked FDA due to the content of the guidance, requiring the following extraordinary actions in the recently enacted Food and Drug Safety and Innovation Act:³¹

"Not later than 18 months after the date of enactment of this paragraph, the Secretary shall submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a report regarding when a premarket notification under subsection (k) should be submitted for a modification or change to a legally marketed device. The report shall include the Secretary's interpretation of the following terms: 'could significantly affect the safety or effectiveness of the device', 'a significant change or modification in design, material, chemical composition, energy source, or manufacturing process', and 'major change or modification in the intended use of the device. The report also shall discuss possible processes for industry to use to determine whether a new submission under subsection (k) is required and shall analyze how to leverage existing quality system requirements to reduce premarket burden, facilitate continual device improvement, and provide reasonable assurance of safety and effectiveness of modified devices."

The law also states "The Secretary shall withdraw the Food and Drug Administration draft guidance entitled 'Guidance for Industry and FDA Staff—510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device', dated July 27, 2011, and shall not use this draft guidance as part of, or for the basis of, any premarket review or any compliance or enforcement decisions or actions."

Congress directed FDA to keep in place the K97-1 guidance until Congress concurred with any new FDA guidance on the issue as noted above.

The upshot of these recent mandatory statutory provisions related to modifications to marketed devices and the need to submit a new 510(k) is that Congress is telling FDA (1) there is a need for industry and

²⁹ Advamed. The 510(k) Process: The Key to Effective Device Regulation, 8/19/08.

³⁰ ODE Annual Report 2008. Special 510(k)s are meant for changes to marketed devices.

³¹ Significant Amendments to FDCA, <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentstotheFDCA/FDASIA/ucm20027187.htm>.

FDA consensus on the definition of terms used in the 510(k) regulation related to modification of devices, suggesting even the K97-1 guidance and processes are unsatisfactory, (2) Congress will not tolerate a stringent or expanded interpretation of when a 510(k) is needed for a change to a device, as was the case in the withdrawn 2011 guidance, and (3) compliance with the QS regulation should be used as a foundation for "reasonable assurance of safety and effectiveness of modified devices."

As noted, by law Congress rejected FDA's "current thinking" on regulation of changes to marketed devices. The future report to Congress on modifications to devices will serve to recalibrate FDA's thinking to Congressional intent. There is the potential Congress may find as too stringent prior FDA decisions to require 510(k)s for some modifications to marketed devices.

In the recent law Congress uses the terms "reasonable assurance of safety and effectiveness" related to regulation of modified 510(k) devices and not "substantial equivalence" thus further blurring the line between premarket approval and premarket notification.

c. How FDA Determines Substantial Equivalence

FDA reviewers in ODE and OIVD primarily use the decision flowchart first described in a 1986 FDA guidance document when determining substantial equivalence and documenting their decision.³²

The document describes the key decision elements in determining substantial equivalence, as follows:

"Thus, as a matter of practice, CDRH generally considers a device to be SE to a predicate device if, in comparison to the predicate device:

the new device has the same intended use (as discussed below); and,

the new device has the same technological characteristics, (i.e., same materials, design, energy source, etc.); or, it has new technological characteristics that could not affect safety or effectiveness; or

it has new technological characteristics that could affect safety or effectiveness, and

-- there are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and

-- there are data to demonstrate that the new technological features have not diminished safety or effectiveness."

The document describes decision aspects when determining whether the new device has the same intended use as the predicate as follows:

"While a new device must have the same intended use as a

³² Guidance on the CDRH Premarket Notification Review Program 6/30/86. (K86-3), 510(k) Memorandum #K86-3: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm>.

predicate device in order to be SE, the Center does not require that a new device be labeled with precise therapeutic or diagnostic statements identical to those that appear on predicate device labeling in order for the new device to have the same intended use. Label statements may vary. Certain elements of a predicate device's labeled indication may not be critical to its intended therapeutic, diagnostic, prosthetic, surgical, etc., use. The Center's scientific expertise enables it to exercise considerable discretion in construing intended uses in the labeling and promotional materials for predicate and new devices. Thus, a new device with the same intended use as a predicate device may have different specific indication statements, and, as long as these label indications do not introduce questions about safety or effectiveness different from those that were posed by the predicate device's intended use, the new device may be found SE.

For the purposes of determining whether or not the new device has the same intended use as a predicate device, the Center assesses any difference in label indications in terms of the safety and effectiveness questions they may raise. The Center considers such points as physiological purpose (e.g. removes water from blood, transports blood, cuts tissue), condition or disease to be treated or diagnosed, professional or lay use, parts of the body or types of tissue involved, frequency of use, etc. If a new device is determined to have the same intended use, the Center may then proceed to determine whether or not it is substantially equivalent. (Devices which do not have the same intended use cannot be substantially equivalent.)"

For technological differences the guidance states:

"Thus, from a scientific perspective, to determine which technological changes are consequential, the Center considers whether:

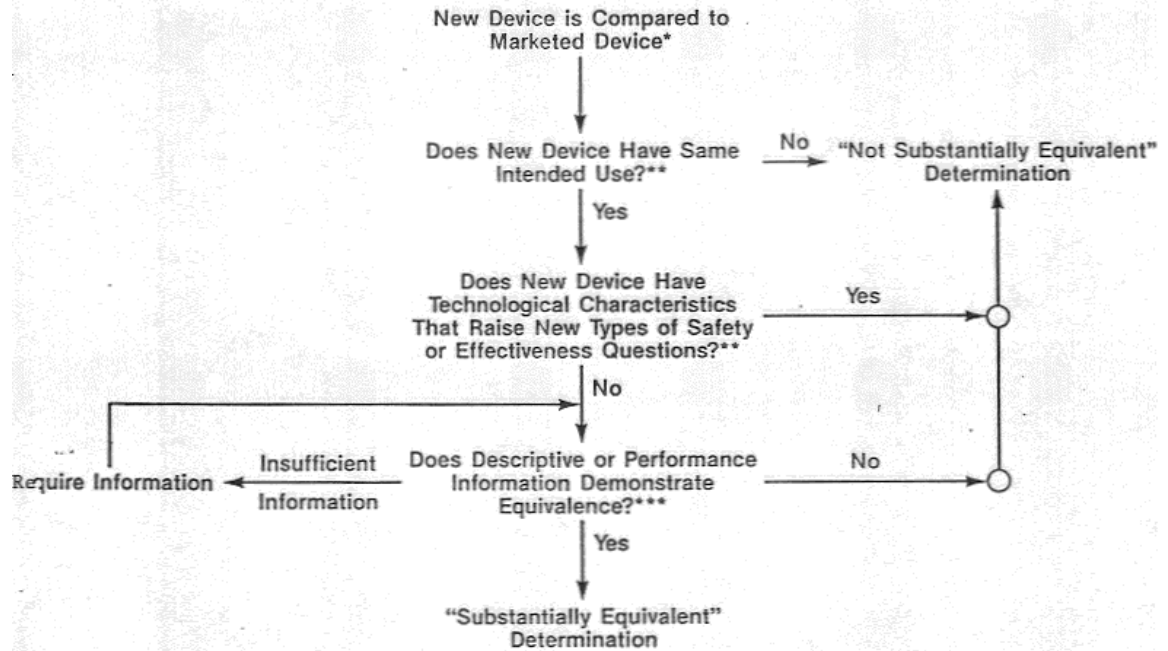
- the new device poses the same type of questions (emphasis added) about safety or effectiveness as a predicate device.;*
- there are accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected as a result of the use of new technological characteristics; and*
- there are data to demonstrate that new technological characteristics have not diminished safety or effectiveness"*

In terms of performance data the guidance notes:

"Typically, 510(k) provides descriptive and testing data that compares the new device to another marketed device within the type, but does not necessarily compare the new device directly to a predicate device. In these cases, the Center can rely, as necessary, on performance data appearing in previously reviewed 510(k) files, in Center classification files, or in the literature, to determine that the device is not only comparable to another marketed device within its type, but is also SE to a predicate device."

The decision tree taken from the guidance and used by FDA and industry for the determination of substantial equivalence and documentation of the decision follows.³³

510(k) "Substantial Equivalence" Decision-Making Process (Overview)



d. Significant Changes to 510(k)s Since 1976 Relating to the Determination of Safety and Effectiveness

Based upon my experience and training I believe that the 510(k) review process is robust and truly is a basis for the determination of the safety and effectiveness of medical devices. The process has evolved to increase the requirements for 510(k) submissions in order to establish a device's reasonable assurance of safety and effectiveness. It certainly provides a considerable hurdle to the marketing of new devices.

The first significant change to the act after 1976 regarding 510(k)s was the Safe Medical Device Act of 1990 (SMDA).³⁴ SMDA increased the authority of FDA and the requirements for manufacturers. The definition of "substantial equivalence" was incorporated into the act, Special

³³ An updated chart posted by FDA and used for documentation purposes (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM081395.pdf>) has essentially the same elements, including the terminology of new "types" of questions regarding technological changes.

³⁴ The Safe Medical Devices Act of 1990 (P.L. 101-629), which amended the FFD&C Act (21 U.S.C. 201 et seq.), was signed into law on November 28, 1990.

Controls were permitted as a substitute for performance standards for Class II devices, devices could be found equivalent to post-76 legally marketed devices not requiring a PMA, a summary of safety and effectiveness was required, preproduction design controls were now regulated, FDA had to issue a 510(k) equivalence order before a device submitted under a 510(k) could be marketed, and correction and removal reports were required. Also, 510(k)s for Class III devices had to now include a summary of adverse data relating to the safety and effectiveness of the device.

The next change was the FDA Modernization Act of 1997.³⁵ FDAMA focused FDA resources on those devices presenting the most risk. FDAMA instituted "Good Guidance Practices" to strengthen the development and vetting of documents to the public. The "least burdensome" principles were also added. In a guidance document³⁶ FDA defined least burdensome as "a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA."

The following change was the Medical Device User Fee Act of 2002. According to FDA, MDUFMA was enacted "in order to provide the Food and Drug Administration (FDA) with the resources necessary to better review medical devices, to enact needed regulatory reforms so that medical device manufacturers can bring their safe and effective devices to the American people at an earlier time..."³⁷

A July 2014 guidance issued by FDA on the determination of substantial equivalence notes "Because devices are classified according to the level of regulatory control necessary to provide a reasonable assurance of safety and effectiveness, classification of a new device through the 510(k) process requires FDA to determine the issues of safety and effectiveness presented by the new device, and the regulatory controls necessary to address those issues."³⁸

The guidance goes on to state "The 510(k) review standard (substantial equivalence of a new device to a legally marketed (predicate device) differs from the PMA review standard (reasonable assurance of safety and effectiveness) in that the 510(k) review standard is comparative whereas the PMA standard relies on an independent demonstration of safety and effectiveness. Nonetheless, the principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review."

³⁵ FDAMA,

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsstotheFDCA/FDAMA/default.htm>.

³⁶ The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Guidancedocuments/ucm085994.htm>.

³⁷ MDUFA,

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109149.htm>

³⁸ Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], <http://www.fda.gov/downloads/MedicalDevices/.../UCM284443.pdf>.

An Institute of Medicine report of 2011 evaluated the 510(k) program. The IOM report did not contend that a 510(k) review does not make a safety and effectiveness determination.³⁹ In response to the IOM report FDA CDRH Director, Dr. Jeff Shuren, stated in a press release on July 29, 2011:

"We appreciate the IOM's report on the 510(k) program, and agree that the public should continue to feel confident in the medical devices on the market today. Medical devices in the U.S. have a strong track record of safety and effectiveness. The 510(k) program has helped support a robust medical device industry in the U.S. and has helped bring lower-risk devices to market for the patients who need them.

FDA believes that the 510(k) process should not be eliminated but we are open to additional proposals and approaches for continued improvement of our device review programs."⁴⁰

6. Postmarket Surveillance, Monitoring Device Experience: Complaints, Medical Devices Reports, Corrective and Preventive Actions

Once a device is marketed FDA continues to monitor its safety and effectiveness. Three FDA regulatory requirements associated with postmarket surveillance, complaint handling, medical device reports, and corrective and preventive action, are closely linked and describe a system for receiving, assessing and taking appropriate action on postmarket signals.

As required by 21 CFR §820.198, Complaint Files, each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit. Such procedures shall ensure that all complaints are processed in a uniform and timely manner, oral complaints are documented upon receipt, and complaints are evaluated to determine whether the complaints represent an event, which is required to be reported to FDA under part 803, Medical Device Reporting.

The manufacturer is required to evaluate complaints and make investigations as needed. Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated, unless such investigation has already been performed for a similar complaint and another investigation is not necessary.

The medical device reporting regulation, 21 CFR §803, establishes the requirements for medical device reporting of events identified in the complaint process for device user facilities, manufacturers, and importers. A manufacturer or importer must report to FDA deaths and serious injuries their device has or may have "*caused or contributed*" to, certain device malfunctions, and they must establish and maintain adverse event files. A manufacturer must also submit specified follow-up.

³⁹ Ralph S. Hall and Michelle Mercer, Rethinking Lohr: Does "SE" Mean Safe and Effective, Substantially Equivalent, or Both? Minn J.L. Sci. & Tech., Vol. 13:2, 2012.

⁴⁰ press release, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2011/ucm265908.htm>.

The term "caused or contributed" by regulation means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure, improper or inadequate design, manufacture, labeling, or user error.⁴¹

According to FDA, "(MDR) Reports are not required when there is information that would cause a person who is qualified to make a medical judgment (e.g., a physician, risk manager, or biomedical engineer) to reach a reasonable conclusion that a device did not cause or contribute to an MDR reportable event. Information that leads to the conclusion that an event is not reportable must be retained in the MDR event files for the time periods specified in Sec. 803.18."⁴²

FDA posts MDRs on the MAUDE database.⁴³ FDA states on its web site, "MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices."

In Subpart J of 21 CFR §820, Corrective and Preventive Action,⁴⁴ also known as CAPA, it is required that each manufacturer establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements, in part, for analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of product that do not meet a specific requirement (i.e., a nonconformity), or other quality problems.

The manufacturer must investigate the cause of nonconformities relating to product, processes, and the quality system, identify the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems, verify or validate the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device, implement and record changes in methods and procedures needed to correct and prevent identified quality problems, and ensure that information related to quality problems or nonconforming product is disseminated to those directly responsible.

So, for example, if a complaint is received concerning a death or injury then the manufacturer is obligated to assess it and determine if an investigation is warranted and whether an MDR report must be submitted. Steps may be taken to mitigate the event and/or likelihood of the event reoccurring based on reestablished CAPA procedures. Outputs of decision-making in CAPA may be a recall, labeling changes, notices to users, or other actions.

FDA inspects manufacturers to ensure compliance with 21 CFR §820, including the complaint, MDR and CAPA processes. It uses the Quality System Inspection Technique (QSIT) guidance⁴⁵ for FDA investigators as one basis for evaluating these processes.

⁴¹ 21 CFR §803.3.

⁴² FR Notice, Vol.60, No.237 (12/11/95), comment 11.

⁴³ MAUDE,
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM>.

⁴⁴ 21 CFR §820.100.

⁴⁵ <http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm>.

III. History and Evolution of Surgical Mesh Products for Treatment of Stress Urinary Incontinence (SUI)

A. SUI and Treatment Options

The following is a partial excerpt describing SUI and treatment options on FDA's web site:⁴⁶

"Stress urinary incontinence (SUI) is a leakage of urine during moments of physical activity that increases abdominal pressure, such as coughing, sneezing, laughing, or exercise. SUI is the most common type of urinary incontinence in women.

SUI can happen when pelvic tissues and muscles, which support the bladder and urethra, become weak and allow the bladder "neck" (where the bladder and urethra intersect) to descend during bursts of physical activity. This descent can prevent the urethra from working properly to control the flow of urine. SUI can also occur when the sphincter muscle that controls the urethra weakens. The weakened sphincter muscle is not able to stop the flow of urine under normal circumstances and when there is an increase in abdominal pressure. Weakness may occur from pregnancy, childbirth, aging, or prior pelvic surgery. Other risk factors for SUI include chronic coughing or straining, obesity and smoking.

It is important for you to consult with your health care provider for proper diagnosis of SUI...

Women have both non-surgical and surgical treatment options to treat SUI...

Surgery to decrease or prevent urine leakage can be done through the vagina or abdomen. The urethra or bladder neck is supported with either stitches alone or with tissue surgically removed from other parts of the body such as the abdominal wall or leg (fascial sling), with tissue from another person (donor tissue) or with material such as surgical mesh (mesh sling). Surgical mesh in the form of a "sling" (sometimes called "tape") is permanently implanted to support the urethra or bladder neck in order to correct SUI. This is commonly referred to as a "sling procedure."

⁴⁶ Stress Urinary Incontinence, <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm284109.htm>. Viewed on January 29, 2016.

The use of surgical mesh slings to treat SUI provides a less invasive approach than non-mesh repairs, which require a larger incision in the abdominal wall. The multi-incision sling procedure can be performed using three incisions, in two ways: with one vaginal incision and two lower abdominal incisions, called retropubic; or with one vaginal incision and two groin/thigh incisions, called transobturator. There is also a "mini-sling" procedure that utilizes a shorter piece of surgical mesh, which may be done with only one incision."

B. Considerations About Surgical Mesh for SUI

FDA provides the following considerations concerning SUI (emphasis added):⁴⁷

"Mesh sling procedures are currently the most common type of surgery performed to correct SUI. Based on industry estimates, there were approximately 250,000 of these procedures performed in 2010.

While all surgeries for SUI carry some risks, it is important for you to understand the unique risks and benefits for surgical mesh slings used in SUI repair.

In order to better understand the use of surgical mesh slings for SUI and evaluate their safety and effectiveness, the FDA held a panel meeting of scientific experts (Obstetrics and Gynecology Devices Panel of the Medical Device Advisory Committee) in September 2011 and conducted a systematic review of the published scientific literature from 1996 to 2011. For surgical mesh slings used for SUI, both the panel and the FDA's review found that:

- The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year. Longer follow-up data is available in the literature, but there are fewer of these long-term studies compared to studies with one-year follow-up.
- The safety and effectiveness of mini-slings for female SUI have not been adequately demonstrated. Presently, it is unclear how mini-slings compare to multi-incision slings with respect to safety and effectiveness for treating SUI. Additional studies may help the agency to better understand the safety and effectiveness of these devices.
- Mesh sling surgeries for SUI have been reported to be successful in approximately 70 to 80 percent of women at one year, based on women's reports and physical exams. Similar effectiveness outcomes are reported following non-mesh SUI surgeries.
- The use of mesh slings in transvaginal SUI repair introduces a risk not present in traditional non-mesh surgery for SUI repair, which is mesh erosion, also known as extrusion.

⁴⁷ Considerations about Surgical Mesh for SUI, <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345219.htm>.

- Erosion of mesh slings through the vagina is the most commonly reported mesh-specific complication from SUI surgeries with mesh. The average reported rate of mesh erosion at one year following SUI surgery with mesh is approximately 2 percent. Mesh erosion is sometimes treated successfully with vaginal cream or an office procedure where the exposed piece of mesh is cut. In some cases of mesh erosion, it may be necessary to return to the operating room to remove part or all of the mesh.
- The long-term complications of surgical mesh sling repair for SUI that are reported in the literature are consistent with the adverse events reported to the FDA.
- The complications associated with the use of surgical mesh slings currently on the market for SUI repair are not linked to a single brand of mesh.

The FDA conducted a review of Medical Device Reports (MDRs) received from Jan. 1, 2008 through Sept. 30, 2011. During this time frame the FDA received 1,876 reports of complications associated with surgical mesh devices used to repair SUI. The most common complications reported through MDRs for surgical mesh slings for SUI repair, in descending order of frequency, include: pain, mesh erosion through the vagina (also called exposure, extrusion or protrusion), infection, urinary problems, recurrent incontinence, pain during sexual intercourse (dyspareunia), bleeding, organ perforation, neuro-muscular problems and vaginal scarring. Many of these complications require additional medical intervention, and sometimes require surgical treatment and/or hospitalization. With the exception of mesh erosion, the above complications can occur following a non-mesh surgical repair for SUI...

While MDRs are a valuable source of information, this passive surveillance system has notable limitations, including the potential submission of incomplete or inaccurate data, under-reporting of events, lack of denominator data (number of implants), and the lack of report timeliness.

C. Information for Health Care Providers for SUI

The FDA web site includes the following information for health care providers for SUI (emphasis added):⁴⁸

- "Obtain specialized training for each SUI mesh placement technique.
- Be vigilant for potential adverse events from the mesh sling, such as erosion.
- Watch for complications associated with the use of the tools used in transvaginal placement of the mesh sling during the surgical procedure, such as bladder perforations.
- Inform the patient about her choice to have incontinence repair with or without a mesh sling. The patient should understand:

⁴⁸ Recommendations for Health Care Providers, <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345221.htm>.

- the likely success of transvaginal SUI surgery with mesh compared to non-surgical treatment options and non-mesh surgery based on the individual patient factors.
- the potential postoperative complications of a mesh sling surgery compared to non-mesh surgery and their effect on quality of life.
- that there is limited information about outcomes after one year.
- whether or not mesh will be used in the repair, and if so, which specific product will be used.
- that a mesh sling is a permanent implant.
- that, as with any SUI surgery, the use of surgical mesh for SUI can make any future surgical repairs more challenging and can put the patient at risk for additional complications and surgeries.
- Ensure that the patient understands the postoperative risks and potential complications of mesh sling surgery.
- Provide patients with a copy of the patient labeling or brochure, if available from the manufacturer"

D. Information for Patients for SUI

The FDA web site contains the following excerpts directed to the patient:⁴⁹

"Ask your surgeon about all SUI treatment options, including non-surgical options and surgical options that do and do not use mesh slings. It is important for you to understand why your surgeon may be recommending a particular treatment option to treat your SUI.

Any surgery for SUI may put you at risk for complications, including additional surgery."

E. The Development of Surgical Mesh for the Treatment of SUI

The FDA Executive Summary from a September 2011 panel meeting provides a brief overview of the development of surgical mesh for the treatment of SUI and pelvic organ prolapse.⁵⁰

"Surgical mesh was a pre-amendments device and was classified into Class II (21 CFR 878.3300). Since the 1950s, surgical mesh has been used to repair abdominal hernias. In the 1970s, gynecologists began using surgical mesh products indicated for hernia repair for abdominal repair of POP, and in the 1990s, gynecologists began using surgical mesh for surgical treatment of SUI and vaginal repair of POP. To do so, surgeons would cut the

⁴⁹ Recommendations for Patients, <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm345230.htm>.

⁵⁰ FDA Executive Summary, September 8, 2011, OB/Gyn Advisory Committee Meeting, page 5, <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/ucm262488.htm>.

mesh to the desired shape for SUI repair or POP repair and then place the mesh through a corresponding incision. Over time, manufacturers responded to this clinical practice by developing mesh products specifically designed for SUI and POP repair.

In 1996, the Surgical Fabrics (ProteGen Sling) device manufactured by Boston Scientific Corporation became the first pre-configured surgical mesh product cleared via the 510(k) pathway for surgical treatment of SUI. (The ProteGen Sling was cleared with an indication for "pubourethral support," a phrase which implies an indication for treatment of SUI.) However, use of mesh in SUI repair, referred to as slings or tape, did not become common until after the introduction of the Tension-Free Vaginal Tape (TVT™) System, manufactured by Ethicon/GYNECARE, in 1998. This system was based on the work by Ulmsten and colleagues with the Ethicon Prolene hernia mesh. In 2002, GYNEMESH® PS, also manufactured by Ethicon/GYNECARE, became the first pre-configured surgical mesh product cleared for POP repair.

Over the next few years, surgical mesh products evolved into "kits" that included tools to aid in the delivery/insertion of the mesh. The first kit for SUI repair, the Island Biosurgical Bladder Neck Suspension Kit manufactured by Island Biosurgical, Inc., was cleared in 1997. The first kits for POP repair, the AMS Apogee™ System and the AMS Perigee™ System, both manufactured by American Medical Systems, Inc., were cleared in 2004. Surgical mesh kits continue to evolve in regards to introducer instrumentation, tissue fixation anchors, surgical technique, and incorporation of absorbable materials into the mesh intended to increase material compliance.

The FDA premarket notification review process did not request original clinical studies to support clearance of surgical mesh indicated for treatment of SUI or POP. Attempts to establish clinical effectiveness were undertaken later by the clinical community with clinical trials, published studies, and systematic reviews/meta-analyses. Some of this published literature was incorporated into later 510(k) submissions to support market clearance.

Premarket clearance of surgical mesh indicated for POP and SUI repair was typically based on pre-clinical bench and animal studies as described in the FDA Guidance Document "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh" issued on March 2, 1999 (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073791.pdf>)."

"From 1992-2010, the FDA cleared 168 510(k)s for surgical mesh with urogynecologic indications."

IV. Ethicon TVT Devices

A. Ethicon Gynecare TVT Product Name Variations

Each of Ethicon's TVT devices are known by other project or product names.⁵¹ In this report, the same device may be identified by one of the alternative names. For example:

Name	Some Alternative Names
TVT	TVT Classic TVT Prolene Mesh TVT Standard
TVT-AA	Abdominal Approach TVT Abdominal
TVT-O	TVT Obturator Mulberry
TVT Abbrevio	TVT Twins
TVT Exact	TVT Retropubic Refresh
TVT Secur	TVT-S TVT Universal Mini sling
TVT-D	TVTD

B. Relevant ETHICON Regulatory Submissions

I examined records provided by counsel to help construct a history table of the ETHICON submissions related to TVT EXACT. I also did a search of the FDA 510(k) database as referenced in the table to identify additional submissions not included in the records provided by counsel. I ordered the submissions by 510(k) number in the table that follows.

The TVT devices intended to treat stress urinary incontinence are under the surgical mesh classification.

Since PROLENE polypropylene is a key constituent of several of the relevant ETHICON devices its first regulatory submission is important. Catherine Beath testified, "there was a pre-amendment Prolene mesh."⁵² A predicate PROLENE polypropylene suture⁵³ was approved by FDA as a drug under NDA 16-374 and later transitioned to the Center for Devices and Radiological Health as a premarket approval. Eight types of sutures, including PROLENE sutures, were reclassified from Class III to Class II devices under 21 CFR §878.5010,⁵⁴ Nonabsorbable polypropylene surgical suture and subject to a special controls guidance document.⁵⁵ This suture is referenced as a predicate for the first vaginal tapes and

⁵¹ DEPO.ETH.MESH.00000067.

⁵² Beath deposition, 3/16/12, page 55:16.

⁵³ see ETHICON submissions table; K940498.

⁵⁴ FR Vol.68, Number 106 (Tuesday, June 3, 2003).

⁵⁵ www.accessfda.gov.

meshes. The history continues with variations of pelvic mesh materials for POP and various vaginal tapes.

K Number	Device Name	Material/Change	Predicate	Data
K962530 ⁵⁶ 8/9/96	PROLENE Polypropylene Mesh Nonabsorbable Synthetic Surgical Mesh	Knitted polypropylene identical to PROLENE sutures Additional sizes and key hole shape	PROLENE polypropylene mesh	Bench, preclinical
K972412 9/10/97	ETHICON PROLENE Polypropylene Mesh Hernia Device Nonabsorbable Synthetic Surgical Mesh Implant ⁵⁷	PROLENE polypropylene	BARD Marlex mesh PerFix Plug	preclinical
K974098 ⁵⁸ 1/28/98	Tension Free Vaginal Tape (TVT) System	Polypropylene mesh identical to PROLENE polypropylene suture	Protegen Sling ⁵⁹ PROLENE Suture NDA/PMA 16-374	Bench, preclinical and clinical data
K984220 2/23/1999	PROLENE (Polypropylene) Hernia System ⁶⁰	Pre-shaped	PROLENE Hernia System	No data indicated in record
K001122 5/23/2000	PROLENE Soft ⁶¹ (polypropylene) nonabsorbable Synthetic Surgical Mesh	Diameter of monofilament and pigmented strands	K962530 and Mersilene mesh (polyester fiber mesh) preamendments	Bench, K962530 preclinical, clinical based on prior Prolene mesh
K002672 11/22/2000	VYPRO Mesh ⁶²	Mix of polypropylene and polyglactin	PROLENE Mesh and VICRYL (polyglactin 910) Mesh	Bench
K010722 4/27/01	Polypropylene 3D Patch ⁶³	Three-dimensional	PROLENE Hernia system and Bard Marlex PerFix Plug	Nonclinical laboratory
K012628 10/26/01	GYNECARE ⁶⁴ Tension-Free Vaginal Tape (TVT) Blue System	Addition of blue pigmented polypropylene fibers interwoven with unpigmented fibers	K974098 K001122	Bench, preclinical, K974098 clinical data
K013718 1/8/2002	GYNEMESH ⁶⁵ PROLENE Soft Nonabsorbable Synthetic Surgical Mesh for Pelvic Floor Repair	Same as K001122 Pelvic floor claim	K001122 K962530 MERSILENE	K00122 for bench testing, K962530 for preclinical, published literature

⁵⁶ ETH-02240-02273.

⁵⁷ accessdata.fda.gov/cdrh_docs/pdf/K972412.pdf.

⁵⁸ 1998 submission, see Attachment.

⁵⁹ Removed from market; no effect on other products based on lack of evidence of FDA action.

⁶⁰ accessdata.fda.gov/cdrh_docs/pdf/K984220.pdf.

⁶¹ ETH-01646-01818.

⁶² accessdata.fda.gov/cdrh_docs/pdf/K002672.pdf.

⁶³ accessdata.fda.gov/cdrh_docs/pdf/K010722.pdf.

⁶⁴ 2001 submission, see Attachment.

⁶⁵ ETH00797-00927.

				for clinical
K031925 9/17/03	PROCEED ⁶⁶ Trilaminare Surgical Mesh	Layers of PS, regular poly, ORC and polydioxanone	PROLENE soft Polypropylene Mesh	Nonclinical and in-vivo testing
K033337	ULTRAPRO Mesh ⁶⁷	No FDA info	No FDA info	Animal testing
K033568 12/8/03	GYNECARE TVT Obturator Device ⁶⁸	New accessories, surgical approach	K974098 K012628 K02356 (sic)	Predicate data
K042603 12/22/04	GYNECARE Prolene Fastener System	Prolene	Mitek meniscal fastener	In-vitro and in-vivo studies
K052401 11/28/05	GYNECARE TVT SECUR System ⁶⁹	Material change and needles fixed to implant; change in implantation method	K033568 K012628 K974098	Bench, Preclinical and cadaver data
K060713 5/25/06	PROCEED ⁷⁰ Surgical Mesh	Change not indicated	PROCEED Trilaminare Mesh	Non indicated
K061533 12/11/06	PROCEED Ventral Patch ⁷¹	Not clear.	PROLENE Soft PROCEED BARD Ventralex VICRYL ETHIBOND	Preclinical, bench and animal
K063562 2/26/07	GYNECARE PROSIMA Pelvic Floor Repair Systems	Precut GYNECARE GYNEMESH PS Mesh Implants and instruments; device balloon assembly; silicon	GYNECARE GYBEMESH PS Nonabsorbable PROLENE Soft Mesh Silimed Vaginal Stent	bench
K070224 4/17/07	ULTRAPRO Plug ⁷²	Plug and patch	ULTRAPRO mesh BARD Mesh PerFix Plug	Bench and animal
K071249 6/5/07	ULTRAPRO Hernia System ⁷³	Change in materials	PROLENE hernia system ULTRAPRO mesh	Bench and animal
K071512 5/15/08	GYNECARE PROLIFT Total, Anterior, and Posterior Pelvic Floor Repair Systems GYNECARE PROLIFT+M Total, Anterior, and Posterior Pelvic Floor Repair Systems ⁷⁴	PROLIFT: Same as GYNEMESH PS; precut mesh and instruments PROLIFT+M: Same as Ultrapro Mesh; precut mesh and instruments	PROLIFT: K013718 AMS Apogee K040537 AMS Perigee K040623 PROLIFT+M: K033337 Ultrapro Mesh K013718 K040537 K040623	Bench, Cadaver, clinical
K082216 9/5/08	ETHICON Mesh ⁷⁵	Absorbable and nonabsorbable polymers	GYNECARE GYNEMESH PS PROLIFT+M	Functional testing
K093932 4/9/10	ETHICON Physiomesh ⁷⁶	Mesh layers, low profile	PROCEED mesh ULTRAPRO Hernia System	Bench and animal

⁶⁶ accessdata.fda.gov/cdrh_docs/pdf3/K031925/pdf.

⁶⁷ www.fda.gov/ohrms/dockets/ac/08/briefing.

⁶⁸ 2003 submission, see Attachment.

⁶⁹ 2005 submission, see Attachment.

⁷⁰ accessdata.fda.gov/cdrh_docs/pdf6/K060713.pdf.

⁷¹ accessdata.fda.gov/cdrh_docs/pdf6/K061533.

⁷² accessdata.fda.gov/cdrh_docs/pdf7/K070224.pdf.

⁷³ accessdata.fda.gov/cdrh_docs/pdf7/K071249.pdf.

⁷⁴ ETH-02015-02238, 01324-01637, 00950-01310, 01903-02014, 01318-01323.

⁷⁵ accessdata.fda.gov/cdrh_docs/pdf8/K082216.pdf.

			ULTRAPRO Mesh	
K100485 3/16/10	GYNECARE TVT Exact Continence System ⁷⁷	accessory changes	GYNECARE TVT	Trocar tests
K100936 7/1/10	GYNECARE TVT ABBREVO ⁷⁸	Change in assembly and accessories	GYNECARE TVT	Bench and cadavers
K113205 6/12/12	ARTISYN Y SHAPED mesh ⁷⁹	Y shaped mesh	ALYTE mesh GYNEMESH M RESTORELLE Y	Mechanical testing
K132054 8/23/13	TVT Exact Continence System	Introducer/tip change	GYNECARE TVT EXACT K100485	bench testing
K141560 10/23/14 Traditional 510(k) ⁸⁰	ETHICON Physiomesb	Macroporous mesh composed of knitted polypropylene, and polydioxanone fibers laminated to absorbable poliglecaprone	K093932 Physiomesb BARD Ventrilo Patch Parietex Mesh	Bench testing per guidance, biocompatibility tests, animal implant test

The following is a description of GYNECARE TVT EXACT Continence System from the TVT EXACT labeling:⁸¹

⁷⁶ accessdata.fda.gov/cdrh_docs/pdf9/K093932.pdf.

⁷⁷ accessdata.fda.gov/cdrh_docs/pdf10/K100485.pdf.

⁷⁸ accessdata.fda.gov/cdrh_docs/pdf10/K100936.pdf.

⁷⁹ accessdata.fda.gov/cdrh_docs/pdf/K113205.pdf.

⁸⁰ Physiomesb,
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K141560>.

⁸¹ ETH.MESH.00020274.

DESCRIPTION

The GYNECARE TVT EXACT™ Continenence System consists of the following sterile, single-use components:

A. GYNECARE TVT EXACT™ Continenence System Trocar Sheath / Implant Assembly
(See Figure 1):

1. Implant
2. Implant Sheath
3. Trocar Sheath
4. Trocar Sheath Cut-out

The GYNECARE TVT EXACT™ Continenence System Trocar Sheath / Implant Assembly consists of one piece of blue (Phthalocyanine blue, color index number 74160)

PROLENE™ Polypropylene Mesh (Implant) approximately 1/2 x 18 inches (1.1 x 45 cm), covered by a clear plastic Implant Sheath and held between two white Trocar Sheaths, which are bonded to the Implant and Implant Sheath. PROLENE Mesh is constructed of knitted filaments of extruded polypropylene strands identical in composition to that used in PROLENE™ Polypropylene Nonabsorbable Surgical Sutures. The Implant is approximately 0.027 inches (0.7 mm) thick. This material, when used as a suture, has been reported to be non-reactive and to retain its strength indefinitely in clinical use. PROLENE Mesh is knitted by a process which interlinks each fiber junction.

B. GYNECARE TVT EXACT™ Continenence System Trocar (See Figure 2):

5. Trocar Handle
6. Trocar Sheath Lock
7. Trocar Shaft

The GYNECARE TVT EXACT™ Continenence System Trocar consists of the stainless steel Trocar Shaft and the plastic Trocar Handle. The Trocar Shaft is designed to fit inside the white Trocar Sheaths on the GYNECARE TVT EXACT™ Continenence System Implant / Trocar Sheath Assembly, and is used to position the GYNECARE TVT EXACT™ Continenence System Implant in the patient from a vaginal incision up through the abdominal wall.

GYNECARE TVT Reusable Rigid Catheter Guide

(available separately – not included in GYNECARE TVT EXACT™ Continenence System)

The GYNECARE TVT Rigid Catheter Guide is a non-sterile reusable instrument intended to facilitate the identification of the urethra and the bladder neck during the surgical procedure. It is inserted into a Foley catheter (recommended size 18 French) positioned in the bladder via the urethra. To facilitate insertion, it can be lubricated with gel.

V. FDA Public Health Actions Concerning SUI

A. FDA Public Health Notification, October 20, 2008.

FDA issued a Public Health Notification (PHN) on Surgical Mesh, following its examination of adverse events related to various surgical meshes sold by numerous different manufacturers.⁸²

The PHN states:

"This is to alert you to complications associated with transvaginal placement of surgical mesh to treat Pelvic Organ Prolapse (POP) and Stress Urinary Incontinence (SUI). Although rare (emphasis added), these complications can have serious consequences. Following is information regarding the adverse events that have been reported to the FDA and recommendations to reduce the risks.

Nature of the Problem

Over the past three years, FDA has received over 1,000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair POP and SUI. These mesh devices are usually placed transvaginally, utilizing tools for minimally invasive placement.

The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia.

Treatment of the various types of complications included additional surgical procedures (some of them to remove the mesh), IV therapy, blood transfusions, and drainage of hematomas or abscesses.

Specific characteristics of patients at increased risk for complications have not been determined. Contributing factors may include the overall health of the patient, the mesh material, the size and shape of the mesh, the surgical technique used, concomitant procedures undertaken (e.g. hysterectomy), and possibly estrogen status.

Recommendations

Physicians should:

⁸² Public Health Notification, <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm>.

- Obtain specialized training for each mesh placement technique, and be aware of its risks.
- Be vigilant for potential adverse events from the mesh, especially erosion and infection.
- Watch for complications associated with the tools used in transvaginal placement, especially bowel, bladder and blood vessel perforations.
- Inform patients that implantation of surgical mesh is permanent, and that some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication.
- Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall (in POP repair).
- Provide patients with a written copy of the patient labeling from the surgical mesh manufacturer, if available."

FDA often provides industry a draft of its public health notice and solicits comments before FDA finalizes the document. Although FDA may consider comments Catherine Beath correctly noted in her testimony "FDA ultimately owns the final version."⁸³

B. FDA Safety Communication, July 13, 2011.

On July 13, 2011, FDA issued an updated safety notice concerning serious complications associated with transvaginal placement of surgical mesh for pelvic organ prolapse⁸⁴ but more information on SUI was still forthcoming (See Section XXX of this report).

C. FDA September 2011 Panel Meeting on SUI Devices

The data supporting the safety and effectiveness of TVT was discussed at the September 9, 2011 meeting of the Obstetrics and Gynecological Panel of the Medical Devices Advisory Committee. While all the data presented do not relate solely to ETHICON devices it is important to understand the overall discussions regarding this type of product.

The Transvaginal Mesh Industry Working Group provided a report, dated August 30, 2011, to the Panel and a presentation summarizing the report was given at the panel meeting. ETHICON participated in the creation of the report and presentation to the panel.

The report describes the advances in surgical mesh devices for SUI beginning with use of autologous tissue, xenografts and allografts and associated concerns for their long-term effectiveness, followed by development of synthetic mesh, retropubic and transobturator approaches and single incision slings. The paper notes "patient selection and surgical technique are critical for the success of any surgical procedure...Physicians must be knowledgeable in pelvic floor anatomy and surgery."

⁸³ Beath deposition, 3/6/12, page 261:24-25.

⁸⁴ <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm>.

The Group reviewed MDR reports. As noted, "This review of the overall MDR rate, as well as rates associated with serious adverse events (SAE), indicated that while there was an increase in adverse events overall, the rate remains low with an average rate of 0.13% for the 2008 to 2010 period. When comparing the number of serious adverse events to the total adverse events for each time period, it was determined that the 2005 to 2007 period had a 33% rate of SAE/Total AE (0.02%SAE) and 2008 to 2010 had a rate of 31% (0.04% SAE). Therefore, the ratio between serious adverse events and total adverse events has remained constant between the two time periods. While the Working Group analysis is still saddled with many of the limitations of the MAUDE database itself, the usefulness of the denominator information allows a better analysis of the change in event rates."

The Group assessed the clinical literature, adverse effects and effectiveness, summarized in appendices to the report, noting "There is strong evidence available to date that demonstrates that the midurethral sling has a favorable benefit/risk profile and that these procedures are valuable treatment options for women suffering from SUI. The risk and benefit is well characterized and understood by the clinical community."

The FDA Executive Summary provided to the panel for the meeting makes states:⁸⁵

"The FDA did not request original clinical performance data for either the first generation minimally invasive suburethral slings or the single-incision mini-slings. A substantial number of quality clinical trials, as well as systematic reviews, have been published for the first generation minimally invasive slings that provide evidence of safety and effectiveness of these devices."

Based on its assessment of the available safety and effectiveness data FDA reported the following conclusions:

"After considering all available data on both safety and effectiveness, and considering the risk/benefit profile, it appears that new premarket clinical trials are not warranted for minimally invasive slings for SUI unless the device has new features (e.g. new polymer or coating) that could affect device performance. The FDA recognizes, however, that the strength of this conclusion is limited by what is largely short duration (2 years) follow-up in the literature with limited data available past 3 years of follow-up.

The FDA believes that new clinical performance data are needed in the premarket setting to ensure the safety and effectiveness of the second generation synthetic slings or "single incision mini slings." The FDA's position is based on the small number of non-randomized studies and two randomized controlled studies which suggest that mini slings may be less effective compared to the first generation minimally invasive synthetic slings. Preliminary

⁸⁵ FDA Executive Summary, September 9, 2011, OB/Gyn Advisory Committee Meeting, <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM270402.pdf>.

safety outcomes suggest that the mini-sling may be associated with greater intraoperative blood loss and lead to higher rates of vaginal mesh erosion compared to first generation slings. Although future randomized controlled trials may lead to different conclusions, the FDA believes that premarket performance data are needed at this time to support market clearance of the second generation synthetic slings.

The regulatory threshold for the FDA to request clinical outcomes data is different for the premarket setting compared to the postmarket setting. The FDA believes that whereas the published literature provides sufficient clinical performance data to support new premarket notifications for the first generation SUI sling, it may be appropriate to require special postmarket surveillance studies to improve the FDA's understanding of the safety profile of all types of minimally invasive slings (including mini-slings).

Finally, the FDA recognizes that all minimally invasive synthetic slings (including mini-slings) are associated with risk of failure as well as patient injury. The FDA believes, however, that the peer reviewed literature affords sufficient understanding of the nature and severity of risks from minimally invasive synthetic slings to enable FDA to review these devices under the Special Controls provisions of 510(k) premarket notification as Class II medical devices. The FDA is not proposing to reclassify these devices from Class II to Class III (Premarket Approval)."

The Panel concluded the following:⁸⁶

Question 1 retropubic and transobturator suburethral slings

The panel consensus was that the safety and effectiveness of these devices is well-established. Unless there are significant material changes or changes in the surgical access (including introducer instrumentation), premarket clinical studies would generally not be necessary. The panel consensus was that consideration should be made to better characterize low frequency life-altering adverse events, potentially via collaboration with industry and use of existing large-scale health databases. The panel did not believe that 522 postmarket studies would be an appropriate mechanism for this, and the consensus was that 522 postmarket studies for these devices are not necessary.

Question 2 single-incision mini-slings

The panel consensus was that the safety and effectiveness of mini-slings is not well understood and that premarket evaluation of new mini-slings should be supported by clinical studies. Such studies should have a control arm of women using a retropubic or transobturator sling with a well-understood risk-benefit profile. The panel believed that the FDA could address this using the 510(k) premarket notification pathway.

⁸⁶ 24 hour memo, <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM271769.pdf>.

The panel consensus also was that, in this case, 522 postmarket studies should address the safety and effectiveness of currently marketed mini-slings. In such 522 studies, the currently marketed mini-sling should be compared to a conventional retropubic or transobturator sling with either a randomized or rigorous cohort design and a 3-5 year follow-up.

D. March 2013 update to FDA website concerning SUI

As noted on FDA's website, on March 27, 2013, the FDA updated the Urogynecologic Surgical Mesh Implant website to include more information for patients about stress urinary incontinence (SUI). This update provides the FDA's current thinking about the use of surgical mesh for repair of SUI and is based on an analysis of adverse events reported to the FDA, findings reported in the scientific literature and input received from the Sept. 9, 2011 meeting of the Obstetrics and Gynecology Devices Panel of the Medical Device Advisory Committee. Additionally, the FDA is following through on our commitment to inform the public about surgical mesh for stress urinary incontinence (SUI).

E. Section 522 Orders

Postmarket surveillance under section 522 of the Federal Food, Drug, and Cosmetic Act (the act) is one means by which the Food and Drug Administration (FDA) can obtain additional safety and/or effectiveness data for a device after it has been cleared through the premarket notification (510(k)) process.

On January 3, 2012 FDA issued 522 postmarket study orders to various mesh manufacturers, including five orders to ETHICON for specific surgical mesh products: GYNEMESH PS, PROLIFT, PROLIFT +M, Prosima and TVT Secur.⁸⁷ The orders requested postmarket surveillance studies and specified the questions to be answered by the studies and elements of the study protocols.⁸⁸ Notably, FDA did not issue any such orders with respect to TVT.

F. FDA Reclassifies Only Surgical Mesh for Pelvic Organ Prolapse Repair in 2016

On May 21, 2014, FDA published a proposal to reclassify surgical mesh for transvaginal pelvic organ prolapse (POP) repair from Class II to Class III.⁸⁹ FDA also proposed to reclassify "specialized" urogynecological surgical mesh instrumentation from Class I to Class II. The FDA proposed order states the mesh reclassification does not include surgical mesh indicated for surgical treatment of stress urinary incontinence, sacrocolpopexy (transabdominal POP repair),

⁸⁷ 522 study listing, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm?start_search=E#E.

⁸⁸ ETH.MESH.030467737-030467740.

⁸⁹ FDA proposed reclassification of POP mesh, and instruments for POP and SUI, <https://www.federalregister.gov/articles/2014/05/01/2014-09907/reclassification-of-surgical-mesh-for-transvaginal-pelvic-organ-prolapse-repair-and-surgical>.

hernia repair, and other non-urogynecologic indications. The proposal includes entirely new classification regulations for mesh used in POP repair and for the specialized urogynecological instruments. FDA published a final order reclassifying surgical mesh for POP repair on January 5, 2016.⁹⁰

VI. Post Panel FDA Action Not Taken on TVT Classic or TVT EXACT; Professional Associations and UK National Institute Support the Safety and Effectiveness of Full-Length/Suburethral/TVT Vaginal Slings

After the FDA panel proceedings on SUI the actions taken by FDA and statements of professional societies and the UK indicate support for midurethral slings for treatment of SUI.

A. FDA Issued no additional special controls for TVT Classic or TVT EXACT

The FDA has never issued any postmarket study order for Gynecare TVT Classic or TVT EXACT and these devices have remained on the market for the last 15 and 5 years respectively. FDA has posted information for patients and providers, which I discuss earlier in this report.

B. January 2014 American Urogynecological Society (AUGS) and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) Statement

On January 7, 2014, AUGS posted a statement entitled "Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence."⁹¹ The statement reads "The polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women." Furthermore it states the following:

"Polypropylene material is safe and effective as an implant."

"The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history."

"Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients."

"The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI."

On March 24, 2014 AUGS and SUFU posted two related documents, one

⁹⁰ 81 FR 353.

⁹¹ <http://www.augs.org/p/bl/et/blogid=16&blogaid=194>.

concerning Frequently Asked Questions by Patients: Mid-urethral slings for Stress Urinary Incontinence and another for Providers.⁹² The statements read, in part:

"The mid-urethral sling is considered safe and effective by the US Food and Drug Administration (FDA). As with any surgery, complications can occur but they are typically minor and can usually be repaired."

"A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of mid-urethral slings as a treatment for SUI [1]."

"The difficulties and complications associated with mid-urethral slings are similar in character to that seen with non-mesh procedures (bladder outlet obstruction, urinary tract injury, dyspareunia, pain, etc.) with the exception of vaginal mesh exposure and mesh perforations into the urinary tract."

"As an implant for the surgical treatment of SUI, macroporous, monofilament polypropylene has demonstrated long-term durability, safety, and efficacy for up to 17 years [5]."

"Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants."

C. March 2013 AUGS Statement

On March 26, 2013, the AUGS published a statement entitled "Position Statement on Restriction of Surgical Options for Pelvic Floor Disorders."⁹³ It reads "The American Urogynecologic Society strongly opposes any restrictions by state or local medical organizations, healthcare systems, or insurance companies which ban currently available surgical options performed by qualified and credentialed surgeons on appropriately informed patients with pelvic floor disorders....Our Justification for this position statement is described below. (parts of justification noted below)

1. A complete restriction on the use of surgical mesh was not the stated intent of the FDA safety communication.
2. The decision on surgical alternatives should be made by the patient and her surgeon.
3. A ban on surgical mesh would prohibit the surgical studies mandated by the FDA and recommended by the NIH, ACOG, and AUGS.
4. In some circumstances transvaginal mesh for pelvic organ prolapse may be the most appropriate surgical option.
5. Any restriction of mesh slings for the treatment of stress urinary incontinence is clearly not supported by any professional organization or the FDA.

However, it is particularly important to note that full-length

⁹² Id.

⁹³ <http://www.augs.org/p/bl/et/blogid=6&blogaid=160>.

midurethral slings were excluded from the (FDA) mandated post marketing studies. In a recent study involving 53 expert urologists and urogynecologists (of whom >90% were fellowship trained) and who could select among many surgical options, the full-length synthetic midurethral sling was the preferred opinion in 93% for the surgical treatment of primary stress incontinence. Full length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard of care for stress urinary incontinence surgery.

6. Any restriction of mesh placed abdominally for the treatment of prolapse is clearly not supported by any professional organization or the FDA.

7. Instead of a ban on mesh we recommend the implementation of credentialing guidelines so that mesh procedures are performed by qualified surgeons.

D. American Urologic Association (AUA) Statement

In November 2011 AUA published a position statement regarding the use of vaginal mesh for the surgical treatment of stress urinary incontinence. It states:⁹⁴

Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-mesh sling procedures as well. It is the AUA's opinion that any restriction of the use of synthetic polypropylene mesh suburethral slings would be a disservice to women who choose surgical correction of SUI.

Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5-10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of follow-up. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional non-mesh sling techniques. The AUA Guideline also indicates that intra-operative cystoscopy should be performed during all synthetic sling procedures to identify urinary tract injury.

⁹⁴ <http://www.auanet.org>.

The AUA strongly agrees with the FDA that a thorough informed consent should be conducted prior to synthetic sling surgery. The AUA also agrees that surgeons who wish to perform synthetic sling surgery should:

- Undergo rigorous training in the principles of pelvic anatomy and pelvic surgery.
- Be properly trained in specific sling techniques.
- Be able to recognize and manage complications associated with synthetic mesh sling placement.

E. National Institute for Health and Care Excellent (NICE); Urinary Incontinence: The management of urinary incontinence in women⁹⁵

The National Institute for Health and Care Excellence (NICE) provides national guidance and advice in the UK to improve health and social care. The September 2013 NICE guidance on treatment of urinary incontinence states the following regarding synthetic tapes:

When offering a synthetic mid-urethral tape procedure, surgeons should: use procedures and devices for which there is current high quality evidence of efficacy and safety...use a device manufactured from type 1 macroporous polypropylene tape...The guideline only recommends the use of tapes with proven efficacy based on robust RCT evidence (emphasis added). However, technological advances are frequent, therefore the choice of tape should include devices that are shown in future clinical trials to have equal or improved efficacy at equal or lower cost. At the time of publication (September 2013) the following met the Guideline Development Group criteria... TVT or Advantage for a "bottom-up retropubic approach.

The guideline does not recommend culposuspension or types of biological slings for the treatment of stress UI. It also provides long-term outcome data to aid the physician in informing their patients.

F. The Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG) Statement

In March 2014 RANZCOG published a position statement on midurethral slings.⁹⁶ The statement reads:

"Mid-urethral slings are minimally invasive procedures developed in the early 1990s to treat female stress urinary incontinence. These slings are narrow, synthetic polypropylene tapes that are surgically placed beneath the middle part of the urethra (water pipe) to provide dynamic support to stop leakage from the bladder. They have been shown to be as effective as more invasive traditional surgery with major advantages of shorter operating and admission times, and a quicker return to normal activities, together with lower rates of complications.³ This has resulted in MUS becoming the operation of choice in Europe, the United Kingdom, Australasia⁴ and the USA⁵ for treatment of SUI.

⁹⁵ NICE guideline:

<http://guidance.nice.org.uk/CG171/NICEGuidance/pdf/English>.

⁹⁶ www.ranzcog.edu.au.

The USA Food and Drug Administration (FDA) released a white paper⁶ and safety communications⁷ regarding safety and effectiveness of transvaginal placement of surgical mesh specifically for pelvic organ prolapse. A prolapse is where some of the pelvic organs bulge downwards giving rise to symptoms of an uncomfortable vaginal lump. Media attention⁸ on this totally distinct and separate issue of mesh use in women has the potential to cause unnecessary confusion and fear in women considering MUS for treatment of stress urinary incontinence. Both RANZCOG and UGSA wish to strongly emphasise that the US FDA publications clearly state that MUS were not the subject of their safety communication.

There is robust evidence⁹⁻¹¹ to support the use of MUS from over 2,000 publications making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use. These scientific publications studied all types of patients, including those with co-morbidities such as prolapse, obesity and other types of bladder dysfunction. It is, however, acknowledged that any operation can cause complications and for MUS, these include bleeding, damage to the bladder and voiding difficulties¹². Nevertheless, the results of a recent large multi-centre trial¹³ have again confirmed the excellent outcomes and low risks of complications to be expected after treatment with MUS. Additionally, long term effectiveness has been demonstrated in studies following patients for up to 17 years.¹⁴⁻¹⁵ In Australia, it has been the operation of choice to treat for female SUI since 2004. RANZCOG and UGSA support the use of monofilament polypropylene mid-urethral sling for surgical treatment of female stress urinary incontinence."

G. 2014 AUGS-Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) Statement

On January 3, 2014, AUGS-SUFU published a joint notice entitled "Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence."⁹⁷ The statement reads, in part, as follows:

The polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women.
Introduction

The purpose of this position statement by the American Urogynecologic Society (AUGS) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) is to support the use of the midurethral sling in the surgical management of stress urinary incontinence, the type of urine leakage generally associated with coughing, laughing and sneezing.

Developed in the early 1990's, midurethral slings (MUS) treat stress urinary

⁹⁷ <http://sufuorg.com/docs/news/AUGS-SUFU-MUS-Position-Statement-APPROVED-1-3-2014.aspx>.

incontinence (SUI) in a minimally invasive, generally outpatient procedure. This technique utilizes a small mesh strip composed of monofilament polypropylene placed through the vagina under the mid-urethra exiting from 2 small sites in either the suprapubic or groin areas.

SUI is a highly prevalent condition of involuntary urine leakage resulting from faulty closure of the urethra typically associated with coughing, sneezing or exertion. SUI is often a debilitating and bothersome condition that can substantially reduce a woman's quality of life. Although non-surgical treatments such as pelvic floor exercises and behavioral modification are helpful in alleviating symptoms in some women [1], many proceed with surgery which is a more effective treatment [2].

In July 2011, the U.S. Food and Drug Administration (FDA) released a white paper [3] and safety communication [4] on the safety and effectiveness of transvaginal placement of surgical mesh specifically for pelvic organ prolapse. In addition, lawyers have publicly advertised their services, targeting women with transvaginal mesh placed for both pelvic organ prolapse and stress urinary incontinence (SUI), and the media has reported on the pelvic organ prolapse mesh litigation. We are concerned that the multimedia attention has resulted in confusion, fear, and an unbalanced negative perception regarding the midurethral sling as a treatment for SUI. This negative perception of the MUS is not shared by the medical community and the overwhelming majority of women who have been satisfied with their MUS. Furthermore, the FDA website states that: "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year." [5].

Justification for the Position Statement

1. Polypropylene material is safe and effective as a surgical implant.

Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. [6, 7] As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years [8].

2. The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history.

A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of the MUS as a treatment for SUI [9]. There are greater than 2000 publications in the scientific literature describing the MUS in the treatment of SUI. These studies include the highest level of scientific evidence in the peer reviewed scientific literature [9]. The MUS has been studied in virtually all types of patients, with and without comorbidities, and all types of

SUI. Multiple randomized, controlled trials comparing types of MUS procedures, as well as comparing the MUS to other established non-mesh SUI procedures, have consistently demonstrated its clinical effectiveness [9-12] and patient satisfaction [12]. Among historical SUI procedures, the MUS has been studied as long in follow-up after implantation as any other procedure and has demonstrated superior safety and efficacy [8]. No other surgical treatment for SUI before or since has been subject to such extensive investigation.

3. Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients.

Since the publication of numerous level one randomized comparative trials, the MUS has become the most common surgical procedure for the treatment of SUI in the US and the developed world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI. There have been over 100 surgical procedures developed for the management of SUI and there is now adequate evidence that the MUS is associated with less pain, shorter hospitalization, faster return to usual activities, and reduced costs as compared to historic options that have been used to treat SUI over the past century. Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard for stress incontinence surgery [13]. Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members [14].

4. The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI.

The midurethral sling was not the subject of the 2011 FDA Safety Communication, *“Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Vaginal Placement for Pelvic Organ Prolapse.”*[3]. In this document, it was explicitly stated: “The FDA continues to evaluate the effects of using surgical mesh for the treatment of SUI and will report about that usage at a later date.” In 2013, the FDA website stated clearly that: “The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year.” [5]

Conclusion

The polypropylene midurethral sling has helped millions of women with SUI regain control of their lives by undergoing a simple outpatient procedure that allows them to return to daily life very quickly. With its acknowledged safety and efficacy it has created an environment for a much larger number of women to have access to treatment. In the past, concerns over failure and invasiveness of surgery caused a substantial percent of incontinent women to live without treatment. One of the unintended consequences of this polypropylene mesh controversy has been to keep women from receiving any treatment for SUI. This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our

organizations which are dedicated to improving the lives of women with urinary incontinence.

On March 24, 2014 AUGS and SUFU posted two related documents, one concerning Frequently Asked Questions by Patients: Mid-urethral slings for Stress Urinary Incontinence and another for Providers.⁹⁸ The statements read, in part:

"The mid-urethral sling is considered safe and effective by the US Food and Drug Administration (FDA). As with any surgery, complications can occur but they are typically minor and can usually be repaired."

"A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of mid-urethral slings as a treatment for SUI [1]."

"The difficulties and complications associated with mid-urethral slings are similar in character to that seen with non-mesh procedures (bladder outlet obstruction, urinary tract injury, dyspareunia, pain, etc.) with the exception of vaginal mesh exposure and mesh perforations into the urinary tract."

"As an implant for the surgical treatment of SUI, macroporous, monofilament polypropylene has demonstrated long-term durability, safety, and efficacy for up to 17 years [5]."

"Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants."

H. November 2015 ACOG/AUGS Practice Bulletin

A November 2015 ACOG/AUGS Practice Bulletin states the following regarding midurethral slings:⁹⁹

Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.

There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.

...

⁹⁸ Id.

⁹⁹ Number 155, November 2015.

Synthetic midurethral mesh slings are the most common primary surgical treatment for stress urinary incontinence in women (67). Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension (68–70). Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings (68). Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings (69). For these reasons, midurethral synthetic mesh slings have become the primary surgical treatment for stress urinary incontinence in women (67, 71). However, in women who decline or are not candidates for synthetic mesh slings, autologous fascial bladder neck slings and Burch colposuspension (laparoscopic or open) remain effective treatment options.

Although controversy exists about the role of synthetic mesh used in the vaginal repair of pelvic organ prolapse, there are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women. For this reason, and to clarify uncertainty for patients and practitioners, the American Urogynecologic Society and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction published a position statement recognizing polypropylene mesh midurethral slings as the “standard of care” in the surgical treatment of stress urinary incontinence (72).

Although there are many ways to place midurethral slings, the main approaches used are retropubic and transobturator techniques. Evidence from a 2015 systematic review demonstrates that these approaches are effective and appear to be comparable in terms of efficacy and patient satisfaction (73). Subjective cure rates up to 1 year after surgery were similar and ranged from 62% to 98% (transobturator route) and 71% to 97% (retropubic route). Short-term objective and long-term (more than 5 years) subjective and objective cure rates also were similar. Voiding dysfunction, bladder perforation, major vascular or visceral injury, and operative blood loss were more common with retropubic slings, whereas groin pain was more common with transobturator slings. Mesh complications (eg, exposures, erosions) were uncommon and did not differ between routes of sling placement (2% overall).

Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.

There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.

VII. Opinions

In forming my opinions, I employed methodologies consistently used by health care companies and regulatory authorities to address and evaluate premarket data, post-approval safety data, risk reduction strategies and labeling obligations. These methods are also consistent with those utilized by me, the sole member of Ulatowski Consulting, LLC, in the conduct of my assignments with both U.S. and international health care clients manufacturing medical devices including preparation of regulatory submissions and post-market efforts, preparation of regulatory and scientific protocols, labeling and other risk mitigation evaluations. My opinions are also predicated upon the Food, Drug, and Cosmetic Act, my numerous interactions with the Federal Trade Commission on device labeling and promotion, the Code of Federal Regulations, Federal Registers, and industry practices and standards.

My participation in this litigation and the development of the opinions enclosed herein follow an extensive review process. As described earlier, I possess extensive experience in the medical device industry and draw on this experience in conducting my tasks under the auspices of Ulatowski Consulting, LLC, including the reviews provided herein.

As described, I have performed a thorough and integrated review of the publicly available information and regulatory documents, including those produced during discovery, identified in this report and listed in Exhibit B. I analyzed those documents for their relevance. The employed methodology also included a review of the production documents, depositions/transcripts, and other materials provided to me by Counsel, or requested by me from Counsel. Upon retrieval, receipt, and review I considered documents for possible inclusion in the evaluation for this report. If additional relevant proprietary documentation was required, and I was unable to independently locate this data/information, I made a request of Counsel for any related documents to be reviewed by me. I analyzed these documents for their regulatory relevance and conformity to industry practices and standards in forming my opinions in the same manner I would have assessed them when I was a premarket evaluator or the chief medical device compliance officer at FDA, and also in the same way I would evaluate them in my current capacity as a consultant to companies on medical device regulatory aspects.

The employed methods also include my reviews of depositions, corresponding exhibits, potentially associated with regulatory affairs, post-market surveillance, device design and manufacturing, and medical services, among others. Reviews of depositions and exhibits are critical. Because I have been engaged in all the aspects of medical device design, development and commercialization, I can interpret and evaluate industry testimony.

Based upon my analysis of these documents and information, as well as my experience, knowledge, and training, I have formed opinions with regard to the Ethicon TVT EXACT. Each of the opinions set forth below is held to a reasonable degree of scientific and regulatory certainty. My prior testimony is listed in Exhibit C. I have no publications in the past 10 years.

I may use visual aids or demonstrative exhibits, such as diagrams, images, slides or charts, to illustrate and or explain my opinions and analyses in this report, as well as excerpts, charts, and other information from the materials I have cited in my report or identified in the materials reviewed.

I reserve the right to supplement this report and my opinions as discovery progresses in this case.

1. It is my opinion that the recall of the Microvasive ProteGen Sling, one of the predicates for the TVT Classic (which in turn is the predicate for TVT EXACT), had no regulatory or safety impact whatsoever on the continued marketing of the TVT Classic or TVT EXACT.

The cleared 510(k) for the Ethicon Tension Free Vaginal Tape (TVT) System, also known as TVT Classic, included the ProteGen Sling, manufactured by Microvasive, a Boston Scientific Company, as one of the predicates for the Ethicon TVT device.¹⁰⁰ The TVT Classic device is the predicate for TVT EXACT.¹⁰¹ The Ethicon TVT System and the ProteGen Sling were similar in that they had the same intended use, clinical mechanism to achieve continence and insertion site, i.e., pubourethral sling to treat stress urinary incontinence by urethral support with incision on the anterior vaginal wall. They also used accessory devices and required anesthesia.

The Ethicon TVT System was different from the ProteGen Sling in several important respects. The material for the Ethicon TVT device is knitted filaments of polypropylene (Prolene) while the ProteGen Sling consisted of woven polyester impregnated with collagen. The collagen ingredient was absorbable. The Ethicon device utilized fixation through the skin while the ProteGen Sling used sutures anchored to bone.

FDA states the following regarding the ProteGen Sling in its Executive Summary to the Obstetrics and Gynecological Devices Advisory Committee on September 9, 2011:¹⁰²

¹⁰⁰ ETH.MESH.00371539-00371542.

¹⁰¹ ETH.MESH.00020258-00020259.

¹⁰² FDA Executive Summary,
<http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmateri>

In 1996, the Surgical Fabrics (ProteGen Sling) device manufactured by Boston Scientific Corporation became the first pre-configured surgical mesh product cleared via the 510(k) pathway for surgical treatment of SUI. (The ProteGen Sling was cleared with an indication for "pubourethral support," a phrase which implies an indication for treatment of SUI.)

Boston Scientific/Microvasive reportedly recalled the ProteGen Sling in January 1999.¹⁰³

Microvasive's voluntary recall of the ProteGen Sling, the sling predicate for the Ethicon TVT System, did not have a regulatory or safety impact on the Ethicon TVT System or TVT EXACT.¹⁰⁴ The safety impact is most important. In my opinion although the ProteGen Sling and the Ethicon TVT device were substantially equivalence by the FDA regulatory standard they were sufficiently different in materials and anchoring to disassociate the ProteGen experience from that of the Ethicon TVT. Also, the post market clinical evidence for the Ethicon TVT device in January 1999 when the ProteGen Sling was recalled and later was demonstrating that the Ethicon TVT device was performing as intended.¹⁰⁵ The 510(k) for the Ethicon TVT System included clinical evidence attesting to its safety and effectiveness.¹⁰⁶ Therefore, there was no safety basis for a recall of the TVT device in January 1999.

Based on the lack of a safety issue, FDA would not have had a regulatory basis to take administrative action on the TVT Classic or TVT EXACT 510(k)s. There is no explicit statutory authority or regulation on vacating a determination of substantial equivalence, or a regulatory method for FDA to rescind a 510(k) determination of substantial equivalence. However, a ruling of a US District Court gives credence to FDA's position that it has the authority to rescind a 510(k), albeit as the court opined in "rare situations" so long as FDA acts in a "reasonable time."^{107,108}

FDA has employed an administrative procedure for rescission but the criterion for rescission by this administrative procedure when the ProteGen was recalled was not applicable to the Ethicon TVT System. Based on my experience, the criterion for rescission was submission by

als/medicaldevices/medicaldevicesadvisorycommittee/obstetricsandgynecologydevices/ucm270402.pdf

¹⁰³ FDA public records of recalls do not extend to 1999. A statement of the status of ProteGen is contained in various publications, e.g., Erosion of Woven Polyester Pubourethral Sling, December 1999, <http://www.ncbi.nlm.nih.gov/pubmed/10569572>.

¹⁰⁴ ETH.MESH.00371496-00371497.

¹⁰⁵ Dr. David Robinson, a medical director at Ethicon, began using the TVT device shortly after it became available. He testified, "Eventually the TVT became the gold standard." Robinson deposition, 7/24/13, Page 45:10-11.

¹⁰⁶ Id., TVT System 510(k).

¹⁰⁷ FDA has considered a future statutory amendment to provide authority for rescission. See "Plan of Action for Implementation of 510(k) and Science Recommendations", <http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm239450.pdf>.

¹⁰⁸ Ivy Sports Medicine, LLC v. Sebellius et al., No 11-cv-1006.

the applicant of incorrect information. An FDA administrative process for rescission of a 510(k) was in a proposed rule that never went final.¹⁰⁹ The expanded rescission criteria in the proposed rule were "information in the 510(k) is incorrect, incomplete, unreliable, or not evaluated properly by FDA in accordance with section 513(f) and (i) of the act." I conclude from my review of the Ethicon TVT System or TVT EXACT 510(k)s¹¹⁰ that none of these expanded criteria applied to the Ethicon 510(k)s.

FDA took no public action to rescind any sling device relying on the ProteGen Sling as a predicate. FDA did not use any other statutory and regulatory remedy at its disposal to remove any Ethicon TVT device from the marketplace due to the recall of the ProteGen Sling. Indeed, FDA cleared several additional Ethicon slings after the ProteGen recall, including, for example, TVT-AA, TVT-O, TVT-Secur, TVT Abbrevio and TVT Exact (see Section IV.B. above for 510(k) listing).

2. It is my opinion that the PROLENE polypropylene material used in the Ethicon TVT devices including TVT EXACT has demonstrated long-term safe and effective performance that supports its continued acceptance as an implantable material. FDA continues to reaffirm its confidence in the safety and effectiveness of PROLENE. It was reasonable and proper and consistent with industry standards and practices for Ethicon to utilize PROLENE in surgical mesh products.

Plaintiffs' complaints and experts allege that PROLENE is biologically incompatible with human tissue. The allegation refers to shrinkage, bacteria, and chemical composition risks and cites a few selected references.¹¹¹ I believe, based on the regulatory and clinical history of PROLENE containing devices, that FDA and the medical community consider PROLENE containing devices, and therefore PROLENE to be clinically acceptable.

The treatment of risks is much more complex than just stating there are risks. There are risks with all implantable materials. Risks can be calculated and mitigated. Residual risks after mitigations, even if significant, can be acceptable based on a benefit/risk assessment. The final value of a device and its materials is based on this process.¹¹²

PROLENE is the primary component in many FDA-cleared Ethicon products including, for example, sutures, mesh, and TVT devices like the TVT Classic and TVT EXACT¹¹³. PROLENE is not a new material. PROLENE Polypropylene Suture (Nonabsorbable Surgical Suture USP, Type B) was first regulated by FDA as a drug prior to the enactment of the 1976 medical device amendments to the Federal Food, Drug and Cosmetic Act. FDA approved a New Drug Application (NDA), NDA 16-374, for Ethicon PROLENE Suture (monofilamentous dyed and undyed) over 45 years ago on April 16, 1969.¹¹⁴ An order approving a new drug is a determination that

¹⁰⁹ 66 FR 3523, 3525 (January 16, 2001).

¹¹⁰ TVT System 510(k), K974098, ETH.MESH.00371496-00371594.

¹¹¹ A PubMed search reveals 5555 published papers using the search term "PROLENE."

¹¹² See ISO 14971, Risk Management standard.

¹¹³ Comparison of TVT Classic to TVT-O, ETH.MESH.08108658 and 00020258.

¹¹⁴ ETH.MESH.09625731-09625737. An NDA for a drug is an equivalent submission to a Premarket Approval application for a device.

the drug is safe and effective.¹¹⁵ The approval for sutures in 1969 made of PROLENE stated the following:¹¹⁶

We have completed the review of this application as amended and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The Investigational New Drug application supporting the PROLENE NDA included an assessment of the safety of PROLENE. Studies were conducted evaluating tissue reactions to PROLENE in the rat, rabbit and dog.¹¹⁷ The full reports were submitted in the NDA as well as other preclinical data.¹¹⁸ The NDA included extensive clinical data, consisting of numerous investigators and subjects.

The NDA file for the Ethicon PROLENE Suture and subsequent submissions, consisting of supplements, amendments and annual reports, is extensive.¹¹⁹ Based upon my 37 plus years of experience at FDA and then consulting, I find the PROLENE suture NDA file to be a comprehensive compilation of medical and scientific evidence supporting the safety and effectiveness of PROLENE since it was marketed in 1969. The information submitted to FDA over the years not only meets the NDA requirements it is also consistent with industry standards and best practices for NDA submissions.

The NDA for PROLENE Suture was transferred from the Center for Drug Evaluation and Research to the Center for Devices and Radiological Health. Ethicon continued to comply with NDA/PMA reporting requirements until those NDA/PMA requirements were transformed to 510(k) requirements by the FDA reclassification of nonabsorbable polypropylene surgical sutures from Class III to Class II.¹²⁰

Besides the approved NDA discussed above, FDA had a major opportunity to assess the safety and effectiveness of PROLENE when it classified surgical mesh. When FDA proposed the classification of the preamendments surgical mesh in 1982¹²¹ it considered the recommendations of the General and Plastic Surgery, Orthopedic, and Gastroenterology and Urology Device Panels. In classifying surgical mesh the Panels relied upon their clinical experience with mesh, their review of published clinical data, and their assessment of the risks posed by mesh to health as stipulated in the act regarding classification procedures.¹²² FDA finalized the classification of surgical mesh, which now includes TVT devices, into Class II in 1988.¹²³

Classification of the mesh by FDA into Class II established that under the law reasonable assurance of safety and effectiveness of surgical mesh would be based upon general controls, including, for example,

¹¹⁵ 21 U.S.C. §355.

¹¹⁶ ETH.MESH.09625731.

¹¹⁷ ETH.MESH.09626043.

¹¹⁸ ETH.MESH.09626242-09626359.

¹¹⁹ Original submission January 17, 1966 supported by IND 1688, 4 original volumes ETH.MESH.00019840-00019846. Subsequent submissions to FDA comprise nearly 50 primary volumes.

¹²⁰ ETH.MESH.09634662-09634663.

¹²¹ 47 FR 2810 (January 19, 1982).

¹²² 21 USC §360c(b)-(d).

¹²³ 53 FR 23856 (June 24, 1988).

510(k) submissions, and any special controls FDA may finalize for the mesh.

I find no evidence in the litigation production, or on FDA's web site of any enforcement action taken by FDA against any PROLENE device or of any recall with a root cause related to the safety or effectiveness of its PROLENE material composition.¹²⁴

Mr. Gregory R. Jones, Director of Regulatory Affairs when the TVT Classic was first marketed, testified regarding the 510(k) submission of TVT to FDA:¹²⁵

"PROLENE mesh is well-known, well understood, been on the market for quite some time. PROLENE sutures had been on the market and well-known and well understood. The testing that had been done over the years on PROLENE Suture and PROLENE Mesh was pretty extensive."

The clinical community is supportive of PROLENE as an implantable material. The January 3, 2014 AUGS-SUFU statement noted in Section V of this report states the following:

"Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. [6, 7] As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years."

The March 24, 2014 AUGS/SUFU statement noted in Section V of this report states the following:

"As an implant for the surgical treatment of SUI, macroporous, monofilament polypropylene has demonstrated long-term durability, safety, and efficacy for up to 17 years [5]."

"Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants."

The table I constructed in this report lists numerous 510(k)s for Ethicon TVTs and mesh devices constructed of PROLENE polypropylene material. Every time FDA cleared one of these TVT or mesh devices it reaffirmed the safety and effectiveness of PROLENE. FDA cannot clear a device it considers to be adulterated or misbranded.¹²⁶

¹²⁴ Recall activities included, for example, instances of counterfeit sutures and delamination reported within limited lots of PROCEED mesh.

¹²⁵ Gregory R. Jones deposition, August 20, 2013, Page 185:19-25.

¹²⁶ 21 CFR §807.100(b)(3).

FDA maintains knowledge of the performance of devices on the market. FDA has posted information regarding TVT on the FDA web and it held a public hearing on TVT in 2011 as noted earlier in this report. There were no concerns regarding PROLENE raised at the open public hearing of the FDA advisory committee by any individual. I am not aware of any petition filed with FDA to remove any PROLENE containing devices from the market. FDA continues to clear TVT devices made of PROLENE, such as the TVT Exact in 2013.

It is evident that FDA and the clinical community believe that the benefits of PROLENE outweigh its risks. The FDA and the medical community's pronouncements I note above in this report make it clear that PROLENE is clinically acceptable as an implantable material and products consisting of PROLENE are reasonably safe and effective for their intended use.

Given PROLENE's long safe and effective history as a material of implanted devices, and the lack of any FDA action to limit its use in devices, it was reasonable and proper and consistent with industry standards and practices for Ethicon to use PROLENE as the material for the TVT-EXACT device.

3. It is my opinion that a change in material or PROLENE weave specifications for the TVT Classic or TVT EXACT would require the submission of a new 510(k) to FDA and clearance by FDA before the modified device could be marketed. This opinion is based on FDA regulations and guidance and is consistent with industry standards and practices.

The composition of the TVT Classic mesh, as described in the original Ethicon 510(k)s cleared by FDA on January 28, 1998, is "knitted filaments of extended polypropylene identical in composition to that used in PROLENE polypropylene suture (Ref. NDA/PMA #16-374).¹²⁷ Ethicon also stated to FDA that the polypropylene strands used to fabricate PROLENE mesh are the same strands used to fabricate PROLENE polypropylene Nonabsorbable Surgical Suture.¹²⁸ The TVT EXACT material is described as follows:¹²⁹

The GYNECARE TVT EXACT™ Continenence System Trocar Sheath / Implant Assembly consists of one piece of blue (Phthalocyanine blue, color index number 74160) PROLENE® polypropylene mesh (Implant) approximately 1/2 x 18 inches (1.1 x 45 cm), covered by a clear plastic Implant Sheath and held between two white Trocar Sheaths, which are bonded to the Implant and Implant Sheath. The mesh implant is approximately 0.027 inches (0.7 mm) thick. The mesh implant is identical to the currently marketed GYNECARE TVT device. The product is not labeled "pyrogen free" or "non-pyrogenic", however the materials have been determined to be non-pyrogenic in previous studies.

Dan Smith, currently an engineering fellow at Ethicon, testified that since the clearance of TVT Classic one clear PROLENE fiber in the mesh

¹²⁷ ETH.MESH.00371539.

¹²⁸ ETH.MESH.08476244.

¹²⁹ ETH.MESH.00020256.

construction was replaced with a blue PROLENE fiber.¹³⁰ He also testified that there was no standard for mesh pore sizes and the mesh construction is measured or defined in courses and wales per inch, not pore size.

Experts for Plaintiffs proffer opinions that the TVT Classic design and material presented safety and effectiveness concerns and Ethicon should have considered alternative materials and designs.¹³¹ For example, Dr. Klinge states on page 37 of his report:

There are alternative design characteristics that would be safer in a woman's pelvic tissues as a treatment for incontinence than some of the design characteristics of the Prolene mesh in TVT. One such safer alternative design would be a mesh product with less material and larger distance between the mesh fibers (Ethicon's Ultrapro mesh has 3-5mm between the fibers and has a weight of 25 g/m2).

Another safer design would be a polymer that elicits a more favorable inflammatory response. PVDF, as a synthetic, non-absorbable suture or mesh material has improved textile and biological properties over polypropylene. It is thermally stable and more abrasion resistant than other fluoroplastics and induces a minimal cellular response, shows exceptional chemical stability and has excellent resistance to aging. PVDF sutures are routinely used in cardiovascular and orthopaedic surgery.¹⁷⁸

On page 18 of his report Dr. Elliot discusses the characteristics of TVT and a "Prolene Mesh Improvement Project." On page 8 of his report Dr. Iakovlev discusses an alternative material called PVDF.

The experts for Plaintiffs do not state whether any of the changes they proffer would be subject to FDA clearance of a new 510(k). The fact is that a new material or significant specifications changes to PROLENE described by Plaintiffs experts would have required a new 510(k).

I assessed the proffered changes as I did for 25 years as a premarket submission evaluator using FDA regulations and related guidance as a basis for my assessment. The FDA regulation for 510(k) submissions, 21 CFR Part 807, requires a new 510(k) be submitted for a marketed device as follows:¹³²

(3) The device is one that the person currently has in commercial distribution or is reintroducing into commercial distribution, but that is about to be significantly changed or modified in design, components, method of manufacture, or intended use. The following constitute significant changes or modifications that require a premarket notification:

- (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.
- (ii) A major change or modification in the intended use of the device.

¹³⁰ Smith deposition, 2/3/14, Pages 721:19-24 and 727:22-25.

¹³¹ Expert Reports 8/24/15, Prof. Dr. Med. Uwe Klinge, Bruce Rosenzweig, MD, Jerry G. Blaivas, MD, Dr. Daniel Elliot, Dr. Vladimir Iakovlev.

¹³² 21 CFR §807.81(a)(3).

FDA guidance provides direction to the industry on the types of changes to an existing device cleared under a 510(k) that may be significant.¹³³ The guidance states the following:

Will the material of the affected part of the implant be likely to contact body tissues or fluids? Changes in materials that contact body tissues or fluids may critically affect the device's safety or effectiveness, either because of potentially new interactions of the device material on the body or because of the body's environmental effects on the new material in the device. Manufacturers should submit a new 510(k) for a change in implant material where the material contacts tissue (including bone tissue) or body fluid.

In addition to the above recommendation by FDA the decision flowcharts in the guidance make it clear that a material change or formulation change, e.g., a weave change, to an implanted device leads to a new 510(k). In addition, Ethicon would be required to verify and validate the changes to the TVT Classic and TVT EXACT as required by the quality system regulation.

Some changes to the TVT Classic or TVT EXACT PROLENE material would not require a new 510(k). Each changed should be preceded by an assessment by Ethicon of the regulatory impact of the change. A change in color of the PROLENE strands, laser cutting or minor changes in the manufacturing process such as those listed in a deposition testimony exhibit¹³⁴ would not require a new 510(k) but would require consideration by Ethicon of the need for verifications and revalidation per the quality system regulation.

4. It is my opinion that there was no reason for FDA to recommend labeling changes to the TVT EXACT. FDA requested changes to TVT Classic labeling, the predicate for TVT EXACT, before clearance in 1998.

FDA evaluates device labeling during the course of a 510(k) review to establish the intended use of the device and to identify other aspects that may need modification to ensure safe and effective use of the device. Once cleared, a device manufacturer may voluntarily modify labeling for several reasons, e.g., to improve it in some manner. Significant changes to labeling affecting safety and effectiveness require clearance by FDA.

From time to time FDA may post information on its web site to health care providers, the industry and the public on public health issues. Any imperative regulatory action directed towards manufacturers is not transmitted by means of these notices but rather through communications directly with the manufacturers.

FDA issued a public health notice in 2008 before the introduction of TVT EXACT. The salutation in the FDA Public Health Notification (PHN) issued October 20, 2008 on gynecological mesh is "Dear Healthcare

¹³³ Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Guidancedocuments/ucm080235.htm>.

¹³⁴ ETH.MESH.10633520.

Practitioner."¹³⁵ It advises physicians regarding training and technique and notably provides three imperatives to physicians to inform patients about risks with the devices. There is no recommendation directed to manufacturers.

The July 13, 2011 update to the PHN was only for transvaginal placement of surgical mesh for treatment of pelvic organ prolapse. A 2013 update to the FDA web site regarding mesh for the treatment of SUI includes information to health care providers and patients. There are no recommendations for manufacturers. Physicians are advised to inform their patients of the risk of using mesh for SUI. Likewise, patients are advised to "ask your surgeon about all SUI treatment options, including non-surgical options and surgical options that do and do not use mesh slings. It is important for you to understand why your surgeon may be recommending a particular treatment option to treat your SUI. Any surgery for SUI may put you at risk for complications, including additional surgery... Ask your surgeon the following questions before you decide to have SUI surgery..."¹³⁶

FDA never recommended any labeling change to an Ethicon TVT device after clearance. FDA requested some labeling changes to TVT System labeling prior to the 1998 clearance including revision to the Indications for Use, Warnings, Adverse Effects, and Instructions for Use. Ethicon generally revised the labeling as requested.¹³⁷

FDA cannot require a labeling change for a 510(k) cleared device but based on the public health notices and FDA's pronouncements there was no reason for FDA to even request such a change.

Ethicon proactively and voluntarily issued new IFUs and patient brochures as I describe in my opinions regarding the IFU and patient brochures. Ethicon also voluntarily revised its labeling in 2013.¹³⁸

5. In regard to the design and manufacturing of the Gynecare TVT devices, Ethicon was proactive in striving to ensure that its complaint and medical device reporting procedures, training of staff on those procedures, implementation, and documentation were substantially compliant with regulations. FDA regulations permit manufacturers to determine whether or not a complaint is a reportable event based on causation. Ethicon's activities were also consistent with industry practices and standards.

Complaint collection and investigation is an important quality management process according to the FDA quality system regulation. Complaints may describe patient-related events that may be reportable to FDA according to the medical device reporting regulation. FDA regulations are not completely prescriptive in how a manufacturer must comply with complaint and reporting requirements. Much of the details in how to construct procedures and policies and work instructions are left to the manufacturer who in turn relies on industry standards and

¹³⁵ ETH.MESH.02252640-02252642.

¹³⁶ Information for Health Care Providers and Patients for SUI, <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh>.

¹³⁷ ETH.MESH.08476217-30.

¹³⁸ <http://hostedv1106.quosavl.com/qb/doc/0nnlfm86hbpkf33bt7pl38flvg>.

practices in meeting the requirements.

In evaluating whether Ethicon met FDA requirements and used industry standards and practices in regard to complaint handling and reporting I examined their procedures and how they implemented those procedures.

Franchise Policy for Product Complaint Management, PL0000087 undated¹³⁹, states, "it outlines the required elements for all complaints relating to ETHICON franchise products to ensure compliance to J&J policy, regulatory requirements, and voluntary standards." It is a high level document and describes the general regulatory elements for complaint and MDR processes. It does not address CAPA except in terms of escalation to CAPA. It is the first revision of the policy¹⁴⁰ put in place in 2010.

A version of the Franchise Complaint Procedure, PR-0000118, version 18,¹⁴¹ put in effect in 2011 provides details on elements of the complaint process described in the above policy. Some of the key elements include certain definitions such as adverse event and incident, minimum information required in a complaint file, complaint investigation, design history review, medical review, serious injuries, deaths and/or incidents. In regard to medical review the procedure states for 5.2.8. "(Medical) Review may be requested to help in determination of device relationship to reported event, to determination of severity of an event for purposes of adverse event reporting."¹⁴² Section 5.2.11.4 states "Medical Assessment: For the reported event, the WCQ Medical Director will write a medical assessment based on the reported complaint information and include one of the following conclusions in the investigation comments (refer to Appendix V for definitions):

- The Device Caused Event
- The Device Contributed to Event
- The Device Potentially Contributed to Event
- The Device Not Likely Related to Event
- The Device is Not Related to Event
- Not Enough Information to Draw a Conclusion

If the Medical Assessment concludes that the device Caused, Contributed to or Potentially Contributed to the Event, then the medical assessment should also include commentary on whether or not the resultant harm is an anticipated outcome of the device or that the outcome is noted in the labeling."

The Franchise Procedure for Summary and Individual Medical Device Reporting, PR551-06, revision 30,¹⁴³ provides detailed procedures for MDR decision-making. It includes summary decision trees including the elements of death and serious injury and malfunction related aspects, and whether the event may be related to the device. It includes consideration whether there is information or medical rationale that states the device did not cause or contribute to a death. It includes aspects not in the MDR regulation but company specified steps such as

¹³⁹ ETH.MESH.03743182-03743193.

¹⁴⁰ Lamont deposition, 4/5/12, page 485:4-7.

¹⁴¹ ETH.MESH.03743365-03743387.

¹⁴² Lamont testifies that this was in place since 2006, Lamont deposition, 4/5/12, page 492:8.

¹⁴³ ETH.MESH.03589458-03589480.

treatment of litigation files, sutures, and packaging.

The April 7, 2013 deposition of Mark C. Yale, manager of worldwide customer quality for Ethicon for a period of time addresses Ethicon's complaint process. Mr. Yale testified on the content of the Ethicon Franchise Instructions for Summary and Individual Medical Device Reporting, PR551-006 Rev.31, 7 Sept 2012.¹⁴⁴

The MDR procedures meet the requirements of 21 CFR Par 803, the MDR regulation in that the multi step reporting decision process includes all the key elements in the regulation such as death or serious injury, intervention, and malfunction determinations. The process includes some Ethicon-specific steps such as steps 4a-4d of revision 31. These variations are permitted by the MDR regulation.

An internal audit of quality system aspects including complaint, MDR and CAPA procedures in 2002, according to Mt. Yale¹⁴⁵ includes observations related to documentation, the need for some clarity in procedures, a few procedural lapses. Internal audits are a requirement of the quality system regulation, 21 CFR §820.22 to help ensure the quality system is in compliance and for continuous improvement purposes. FDA does not inspect these audit reports or any CAPAs initiated due to these audits in order to encourage self improvement by a company.

Deposition records indicate that Ethicon is committed to proper training of staff and reporting compliance as evidenced by several staff emails.¹⁴⁶

The MDR regulation requires manufacturers to assess complaints and to report events that reasonably suggests that a device they market for "may have caused or contributed to a death or serious injury; or has malfunctioned and this device or a similar device that you market would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur."¹⁴⁷

Caused or contributed means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of:¹⁴⁸

- (1) Failure;
- (2) Malfunction;
- (3) Improper or inadequate design;
- (4) Manufacture;
- (5) Labeling; or
- (6) User error.

Manufacturers are required to have staff with the education, background, training and experience necessary to adequately perform

¹⁴⁴ ETH.MESH.07277675-07277696

¹⁴⁵ Yale deposition, 2013, page 151:11

¹⁴⁶ ETH.MESH.01949198-01949200, ETH.MESH.03531443-03531448, ETH.MESH.01814250-01814252, ETH.MESH.00318881-00318889, ETH.MESH.00874613-00874615, ETH.MESH.06496130-06946134

¹⁴⁷ 21 CFR §803.50(a)(1)(2).

¹⁴⁸ 21 CFR §803.3.

their required duties.¹⁴⁹ Ethicon complaint/MDR procedure included the option to obtain Medical Director input on a complaint to determine reportability.

In the deposition testimony of Mark Yale three events are discussed that were not reported due to the conclusions of Charlotte Owens, the Medical Director at that time.¹⁵⁰ Not being a clinician I will not render a medical opinion on her conclusions but note that her input and conclusions are permissible according to the MDR regulation.

Ethicon's efforts regarding its procedures were also consistent with industry standards and practices. The FDA quality system regulation provides the framework for a quality management program but it is industry standards and practices that Ethicon also used to implement the regulation.

6. It is my opinion that the Instructions for Use for the TVT Classic and TVT EXACT are substantially compliant with regulatory requirements, claims are adequately supported, and labeling meets industry standards and practices.

I examined the following Instructions for Use (IFUs) for TVT Classic and TVT EXACT:

IFU Number	Bates ETH.MESH	Content Per Regulation
TVT Classic	05225354- 05225385	Indications, contraindications, warnings, precautions, adverse reactions, actions, how supplied, storage, instructions for use, Rx statement
TVT B	02340306- 02340369	Ditto
TVT C	02340471- 02340503	Ditto
TVT D	05222673- 05222704	Ditto
TVT E	02340504- 02340567	Ditto
TVT	03427878- 03427945	Ditto
TVT EXACT A	02341119- 02341202	Ditto
TVT EXACT	Ethicon website	Ditto

The labeling up to 2015 includes extensive instructions for use, and extensive warning and precautions including the following information:

¹⁴⁹ 21 CFR §820.25(a).

¹⁵⁰ ETH.MESH.03575123, ETH.MESH.03575101, ETH.MESH.03575054.

CONTRAINDICATIONS

As with any suspension surgery, this procedure should not be performed in pregnant patients. Additionally, because the PROLENE Mesh will not stretch significantly, it should not be performed in patients with future growth potential including women with plans for future pregnancy.

WARNINGS AND PRECAUTIONS

- Do not use GYNECARE TVT EXACT™ Continence System on patients who are on anti-coagulation therapy.
- Do not perform the GYNECARE TVT EXACT™ Continence System procedure on patients who have a urinary tract infection.
- Users should be familiar with surgical technique for SUI Sling placement and should be adequately trained in implanting the GYNECARE TVT EXACT™ Continence System before employing it. It is important that the Implant be located without tension under mid-urethra.
- Acceptable surgical practice should be followed for the GYNECARE TVT EXACT™ Continence System procedure as well as for the management of contaminated or infected wounds.
- The GYNECARE TVT EXACT™ Continence System procedure should be performed with care to avoid large vessels, nerves, bladder and bowel. Attention to local anatomy and proper passage of the Trocar Sheaths will minimize risks.
- Retropubic bleeding may occur post-operatively. Observe for any symptoms or signs before releasing the patient from the hospital.
- Cystoscopy should be performed to confirm bladder integrity or recognize a bladder perforation.
- The Rigid Catheter Guide should be gently pushed into the Foley catheter so that the catheter guide does not extend into the holes of the Foley catheter.
- When removing the Rigid Catheter Guide, open the handle completely so that the Foley catheter remains properly in place.
- Do not remove the Implant Sheath until the Implant has been properly positioned.
- Ensure that the Implant is placed with minimal tension under the mid-urethra.
- PROLENE Mesh in contaminated areas should be used with the understanding that subsequent infection may require removal of the material.
- The patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent.
- Since no clinical experience is available with vaginal delivery following the GYNECARE TVT EXACT™ Continence System procedure, in case of pregnancy delivery via cesarean section is recommended.
- Post-operatively, the patient is recommended to refrain from heavy lifting and/or exercise (i.e. cycling, jogging) for at least three to four weeks and intercourse for one month. The patient can return to other normal activity after one or two weeks.
- Should dysuria, bleeding, or other problems occur, the patient should be instructed to contact the surgeon immediately.
- All surgical instruments are subject to wear and damage under normal use. Before use, the instrument should be visually inspected. Defective instruments or instruments that appear to be corroded should not be used and should be discarded.
- As with other incontinence procedures, de novo detrusor instability may occur following the GYNECARE TVT EXACT™ Continence System procedure. To minimize this risk, make sure to place the Implant tension-free in the mid-urethral position.
- Do not contact the PROLENE Mesh with any staples, clips or clamps, as mechanical damage to the mesh may occur.
- Do not resterilize the GYNECARE TVT EXACT™ Continence System. Discard opened, unused devices.

The adverse reactions section in all the above IFUs for the TVT Classic and EXACT up to 2015 include the following:

ADVERSE REACTIONS

- Punctures or lacerations of vessels, nerves, bladder or bowel may occur during needle passage and may require surgical repair.
- Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation.
- As with all foreign bodies, PROLENE mesh may potentiate an existing infection. The plastic sheath initially covering the PROLENE mesh is designed to minimize the risk of contamination.
- Over correction i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction.

All the IFUs meet the regulatory requirements for prescription labeling in that all the IFUs have the required prescription labeling elements.¹⁵¹

On May 2015 Ethicon revised the labeling for the Gynecare TVT family of products.¹⁵² The revised labeling adds a Patient Factors section and expands the adverse effects section compared to prior versions.

I defer to the testimony of Ethicon Medical Directors' clinical opinions regarding the scope, content and interpretation of the listed adverse reactions.

Catherine V. Beath, VP QA/RA at Ethicon, testified regarding the role of the medical directors in deciding the content of labeling:¹⁵³

"...all of the medical directors that I knew that were in the business actually implanted these devices, they had done procedures, so they were the best experts to tell us when it would be appropriate for other physicians like them where the information would be useful."

Labeling statements for PROLENE containing devices have their origin in the NDA for PROLENE sutures. For example, FDA approved a 1988 label for the suture that included warnings related to "minimal, transient acute inflammatory reaction" that basically tracks with the TVT labeling.

In sum, the labeling meets the requirements of the labeling regulation. I do not believe labeling for implantable devices can describe all commonly understood general surgical risks. The labeling is not intended to be a textbook of gynecological surgery. The labeling notes the importance of use of TVT Classic and EXACT only by physicians trained in the treatment of stress urinary incontinence and specifically in implanting the TVT Classic and EXACT. In many respects training, mentorship and publication currency are more important than labeling since it is common knowledge that labeling is not the primary resource of information for a doctor concerning a device.

Industry standards prescribe the contents of device labeling and set forth various mandatory elements, which must be in a device label.

¹⁵¹ 21 CFR §801.109.

¹⁵² www.ethicon.com.

¹⁵³ Catherine V. Beath deposition, July 11, 2013, Page 198:19-24.

This includes indications for use, warnings, and potential adverse events, among other information. Industry standards dictate that labeling cannot be false or misleading. Ethicon's labeling for TVT EXACT contained all of the elements and components required by industry standards, and it was neither false nor misleading in any of the information presented. It is my opinion that labeling for TVT EXACT conformed to industry standards and practices at all times.

7. It is my opinion that Ethicon's risk management policies, processes and procedures and documentation related to TVT EXACT were substantially compliant with regulations, guidance and industry practices.

The quality system regulation requires manufacturers to conduct a risk analysis, where appropriate, as part of design validation.¹⁵⁴ There is no FDA requirement that manufacturers comply with ISO 14971, an international risk management standard, to use as a basis for the risk analysis or to document in a risk report anything other than the risk analysis.

With that said, in my experience, virtually all device manufacturers, including Ethicon, voluntarily adopt a complete risk management program because risk management throughout the life cycle of a medical device has become an industry standard. A complete risk management program is required in order to market a device in many jurisdictions outside the USA such as Europe and Canada.

I examined several Ethicon risk management related records. Some are not specific to Gynecare TVT but are indicators to me of Ethicon's approach to risk management for all of its devices. The procedures include the following:

Franchise Procedure for Medical Device Risk Management Plan, PR602-003, Revision 20.¹⁵⁵ The process includes the standard elements of risk analysis, risk evaluation, risk control, residual risk evaluation, evaluation of production and postproduction information, and reassessment of risk as needed during the life cycle of the product.

Franchise Procedure for Post Market Surveillance, PR-0000385, Revision 5 (two versions).¹⁵⁶ This process is referenced in the Risk Management Procedure noted above. Daniel J. Lamont, director of postmarket surveillance, testified that these were not necessarily the final versions in the Ethicon system¹⁵⁷ but I believe they are at least relevant indicators of Ethicon's process. The PMS plan includes collection and assessment of postmarket signals from a variety of sources, risk categorization, escalation of issues as needed, and follow up.

Operating Procedure for Failure Modes and Effects Analysis Application (aFMEA) or Design (dFMEA), OP650-011, Revision 14.¹⁵⁸ The process

¹⁵⁴ 21 CFR §820.30(g).

¹⁵⁵ ETH.MESH.03742413-439.

¹⁵⁶ ETH.MESH.06773111-130 and 06774005-030.

¹⁵⁷ Daniel J. Lamont, deposition April 3-4, 2013, Page 99:17-23 and 133:15-18.

¹⁵⁸ ETH.MESH.03742801-835.

includes determination of a risk priority number, assessing that RPN according to risk categories, taking action to reduce risk, when necessary, and reassessing the risk after action.

Device Design Safety Assessment (DDSA) Summary Report, TVT Obturator, December 2003, with a summary report of the medical impact and benefit, qualitative and quantitative characteristics with relevance and comments noting the response, hazard worksheet, assessment forms, criteria and assignment of risk level.¹⁵⁹

DDSA Version 2, for components of the TVT Obturator describing the medical impact and benefit of the device and an assessment of the characteristics, whether the characteristic is applicable and a response is needed, and comments describing the response.¹⁶⁰

Device Design Safety Assessment (DDSA) Re-evaluation for TVT, updates the DDSA completed by Medscand in 2000 for the TVT Classic. As noted, it assesses 11 hazards not identified in the 2000 DDSA, and reassesses a newly identified pull off hazard based on MDR reportable complaints and other complaint trends.¹⁶¹

Mr. Lamont, director of postmarket surveillance at Ethicon, provided clear and thorough deposition testimony regarding Ethicon's postmarket procedures. He stated, for example:

So typically or historically the quality engineers would be responsible in that first...one year or two years post launch of a product. And they would assess whether the product was stable in the marketplace. So they would look at the complaints that were coming in and compare it against the risk profiles that they had worked on prior to launch and...ascertain how the product was performing¹⁶²

Q: From a postmarketing surveillance point of view, when you are assessing the performance of the TVT family of products, what are the sources of information that you intake into the process?

A: So complaints and adverse events. We would also look at internal NCRs...any CAPAs...if there are any products or issues we've had to escalate, we have a process called PQI...if we had any field actions...our medical affairs organization performs literature searches...if there was any sort of customer feedback...It could also include sources such as postmarket clinical trials that might be performed. It could include any type of benchtop testing...it could also include something like an independent postmarket trial.¹⁶³

He states in regard to complaints: "So for the TVT family of products, generally speaking, we have very stable rates of complaints and adverse events reported."¹⁶⁴

¹⁵⁹ ETH.MESH.00222401-00222406.

¹⁶⁰ ETH.MESH.01808687-01808698.

¹⁶¹ Contained in TVT design history file ETH.MESH.01317508-613.

¹⁶² Daniel J. Lamont deposition, 4/3/13, Page 52:13-23.

¹⁶³ Id. Page 69:6 to 70:10.

¹⁶⁴ Id. Page 211:17-19.

He states, in regard to medical rationale for not reporting a complaint: "That would come between the analyst and likely Dr. Chen and the group. So that would—that determination itself wouldn't be done independently without medical."¹⁶⁵

I find these procedures and reports are all consistent with ISO 14971/2007, in that all the elements of the standard are addressed in the risk management processes in Ethicon. The processes are substantially compliant with the FDA requirement for a risk analysis for each type of product. Mr. Lamont's testimony demonstrates a high degree of integration of risk management into Ethicon's operating procedures.

8. In regard to the design, manufacturing, testing and marketing of the Gynecare TVT Classic and TVT EXACT, Ethicon substantially complied with all FDA premarket and related quality system requirements prior to and during marketing for the TVT Classic and TVT EXACT including, for example, 510(k) and design control requirements. Ethicon's launch and continued clinical use of the TVT Classic and TVT EXACT was supported by clinical assessments of benefit vs risk.

In general, FDA regulations require a new device to be cleared or approved, unless otherwise exempt from such requirements, before it can be marketed.¹⁶⁶ In this report I document the 510(k) clearances for the listed Ethicon TVT devices. FDA concluded that the devices were all substantially equivalent to predicate Class II devices.

FDA regulations permit a manufacturer to make changes to a cleared device without submitting a 510(k) if the manufacturer concludes that the change could not significantly change or modify the device in design, material, chemical composition, energy source or manufacturing process.¹⁶⁷ In my experience it is common that manufacturers make changes to their devices or manufacturing processes and document their decisions regarding these types of changes during the course of marketing their devices.

I evaluated the Gynecare TVT and TVT EXACT Clinical Expert/Evaluation Reports and 510(k)s to identify the validations performed prior to marketing the TVT devices, and the benefit/risk assessments as follows:

Section 5 of K974098¹⁶⁸ documents clinical data from Ulmsten and a multi-center Scandinavian study, both using a Prolene sling,¹⁶⁹ and additional clinical literature. The June 15, 2000, Clinical Expert Report by Richard A. Isenberg, M.D. for TVT lists the primary and secondary benefits of TVT and side effects.¹⁷⁰ His risk-benefit analysis concludes that the benefits of TVT usage outweigh the risks. Supplemental analyses provided by Petra Kohler, Dan Smith and Martin Weisberg support modifications to the original device.

¹⁶⁵ Id. Page 274: 11-14.

¹⁶⁶ 21 CFR §807.81 and 21 CFR §814.1.

¹⁶⁷ 21 CFR §807.81(a)(3).

¹⁶⁸ ETH.MESH.00371496-00371514.

¹⁶⁹ Ulmsten describes Prolene tape dimension as 40cm long and 10mm wide.

¹⁷⁰ ETH.MESH.07226579-590.

A Clinical Evaluation Report,¹⁷¹ August 2, 2010, by Dr. David Robinson includes assessment of data and information on the TVT Classic to that point in time, including literature, complaint/adverse effect data, labeling, and risk/benefit analysis. Dr. Robinson concludes there were no additional harms/hazards compared to labeling and the internal complaint database.

Piet Hinoul testified comparing a TVT patient brochure and claims of low-risk, minimally invasive and rare complications compared to the Burch procedure:¹⁷²

"And certainly if you hold the data on this device to what we used to do in the past, being the Burch colposuspension, where patients would have to go in the hospital for a week, undergo a big cut in the abdomen, a laparotomy, a very difficult procedure to learn, very difficult procedure to recover from. So I would absolutely agree with what is stated in that brochure."

Dr. David Robinson testified regarding the Burch procedure compared to TVT:¹⁷³

"Eventually the TVT became the gold standard."

A May 28, 2010 Clinical Expert Report by Dr. Aaron K. Kirkemo, Associate Medical Director at Ethicon assessed whether essential requirements were met to enable the marketing of TVT EXACT in Europe.¹⁷⁴ Since TVT Classic is the predicate it is valid that safety and effectiveness data on TVT Classic would form the basis of a benefit/risk analysis for TVT EXACT. The report assesses the current literature and complaint profile for TVT Classic. The report concludes that the essential requirements were met and no clinical data was needed for TVT EXACT. The report includes a comparison of TVT Classic to TVT EXACT as follows:

COMPARISONS between GYNECARE Tension-free Vaginal Tape (TVT) System and The GYNECARE TVT EXACT™ Contenance System.

Both systems use the same laser cut polypropylene mesh implant as the laser cut GYNECARE Tension-free Vaginal Tape (TVT) System. Both implant sleeves are the same design and material. Save for the means of attaching the implant/implant sheath and the trocar sheath to the trocar shaft (EXACT) versus implant/implant sheath and trocar needle to the trocar handle the IFU's are identical. EXACT requires one less cystoscopy. The needle tip radiuses are identical as are the curvature of the trocar sheath/trocar compared to the Classic TVT needle. The TVT EXACT trocar sheath is 4.2 mm versus 5.0 mm for the TVT "Classic" device. Hence it was felt that review of the "Classic" GYNECARE Tension-free Vaginal Tape (TVT) System safety and efficacy data would be sufficient to assess the value of the new system relative to competitive retropubic devices as well as for the alternative surgical approaches for management of SUI.

A July 16, 2013, Clinical Evaluation Report by Dr. Piet Hinoul, Medical Director at Ethicon, assesses the benefit/risk profile for the TVT family of products including TVT EXACT.¹⁷⁵ The report concludes:

¹⁷¹ ETH.MESH.00831361-00831400.

¹⁷² Hinoul deposition, 6/27/13, page 411:6-14.

¹⁷³ Robinson deposition, 7/24/13, page 45:10-11.

¹⁷⁴ ETH.MESH.01269170-01269207.

¹⁷⁵ ETH.MESH.10683482-10683816.

The literature review data, taken together with previously available clinical and pre-clinical data, are sufficient to demonstrate State of Art compliance with the essential requirements covering safety and performance of the GYNECARE TVT™ Family of products under normal conditions of use. No additional clinical data is required. No previously unidentified harms or hazards were identified in this review.

No information was provided from either the literature or PMS data to indicate that any new performance issues are occurring in the clinical setting that were previously unknown.

After manual review and analysis, no new hazards, increased risk or unexpected adverse events were noted. The clinical evidence provides support that GYNECARE TVT™ meets the Essential Requirements of the Medical Device Directive 2007/47/EC.

The design control regulation requires procedures for design and development planning, design inputs, design outputs, design review, design verification and validation and design transfer.¹⁷⁶ The design history file "contains or references the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of (the quality system)."¹⁷⁷ The design control file for the TVT-O device,¹⁷⁸ inasmuch as it is evidence of Ethicon's execution of design control requirements for all its TVT devices, is complete and comprehensive as evidenced by sections and thorough records relating to all the above requirements.

Mr. Smith testifies:¹⁷⁹

Q: "Is there also a design history file for TVT Blue?" (question repeated for TVT-AA, TVT-O, EXACT, SECUR, TVT D)

A: "Yes"

He also testifies:¹⁸⁰

Q: "So for the TVT Classic is there a design history file? Does Ethicon have a design history file for the TVT Classic?"

A: "To the best of my knowledge, there's documentation for every one of these products."

I have evaluated the ETHICON documents that would be included in a design history file for TVT Classic.¹⁸¹ Records comprising a Design History file need not be maintained in one location.¹⁸² The Design Control requirements of the Quality System Regulation became effective until June 1, 1997 and FDA provided a grace period for manufacturers to comply with this portion of the Quality System Regulation until June 1, 1998. For those devices already on the market FDA did not intend for

¹⁷⁶ 21 CFR §§820.30(b)-(h).

¹⁷⁷ 21 CFR §820.30(j).

¹⁷⁸ Smith deposition, 5/15/13, Exhibits T217, T223-228.

¹⁷⁹ Smith deposition, 5/15/13, pages 108:6-109:11

¹⁸⁰ Id. page 95:21-25.

¹⁸¹ ETH.MESH.01317508-613.

¹⁸² 21 CFR §820.30(j).

Design Controls to be retroactive.¹⁸³ Since TVT Classic was cleared on January 28, 1998 Ethicon was not required to have a Design History file for this device at that time.

9. In regard to the design, manufacturing, labeling and marketing of the Gynecare TVT EXACT device, the Issue Reports and the associated Medwatch reports are indicative of Ethicon's substantial compliance with complaint and MDR regulatory requirements.

I examined the following Issue and Medwatch (MDR) Reports for Ethicon Gynecare TVT EXACT dated March 21, 2013:

Device	Type Report	Open Dates	Pages	First Starting Dates
TVT EXACT	Issue	9/2010-2/2012	201	02652318
TVT EXACT	Medwatch	as above	321	03652324
TVT EXACT	MDR	2012-2015	577 reports	N/A

A single Ethicon internal Issue Report is approximately 8 pages while a single Medwatch Report to FDA is 2 or 3 pages for the FDA Medwatch Form 3500A.

I have the following observations from my review of these reports:

1. Ethicon Issue Reports document complaints, their investigation by Ethicon, and Ethicon's decisions determining whether a complaint is reportable to FDA.
2. The Issue Reports document complaints concerning procedure and post procedure related events. The procedure complaints include "out of box" problems like packaging problems, device malfunctions during the procedure like loose mesh, tip or needle bending or breakage, and procedural issues. The post procedure events reported as MDRs include, for example, bladder perforation, pain, urination problems, tip breakage or bending, hematoma and erosion.
3. Events not resulting in MDRs generally include those where there was no patient effect reported.

I reviewed a Complaint Vigilance Audit Report dated February 2002¹⁸⁴ and an Independent MD&D Sector Audit of Ethicon MDR process in 2012.¹⁸⁵ These internal audits are required by regulation but are not inspected by FDA. The audits are part of the continuous improvement process in a company. The purpose of the audits is to make observations of a system which the company can then improve. I agree with Catherine V. Beath who testified regarding these audits:¹⁸⁶

¹⁸³ Preamble to QSR, comment 64, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/ucm230127.htm>.

¹⁸⁴ ETH.MESH.02249640-642.

¹⁸⁵ ETH.MESH.07724068-080.

¹⁸⁶ Beath deposition, 7/12/13, pages, 561:23-24 and 569:4-7.

"I'm confident we had a plan to address them (the identified issues). You're always trying to improve."

"But this (the 2012) audit basically said the reporting decisions are consistent with regulations and FDA guidance. The information and rationale to support a decision is sometimes inadequate."

She also testified:¹⁸⁷

"Based on a number of inspections that they (FDA) have done at the Somerville facility, almost always of the complaint MDR system, I think they're pretty confident that we follow the regulations and that when we find we have gaps, we correct them. As a matter of fact, they've told us that, that they have a lot of confidence in Ethicon to correct problems."

I examined the FDA MAUDE database for 2012 through 2015 for additional MDR reports.¹⁸⁸ There was a surge of 479 MDRs in 2014 from a minimal baseline of less than 20 per year before 2014 and 65 reports in 2014, likely due to the effect of FDA activity on pelvic organ prolapse and stress urinary incontinence devices and subsequent increase in litigation.

In sum, based on my observations, the internal audit reports, lack of FDA enforcement action regarding Ethicon's complaint and MDR procedures, and considering the regulatory requirements for complaint handling and medical device reporting I find them supporting Ethicon's substantial compliance with those requirements.

10. In regard to the design and testing of the Gynecare TVT retropubic device, the clinical evidence supporting the safety and effectiveness of Ethicon TVT devices were of a sample size and duration consistent with clinical evidence in other 510(k) devices and even with several PMA approved devices.

During the course of my career at FDA and now as a consultant I have created clinical protocols and evaluated clinical protocols and data used to support the marketing of medical devices.

In the 510(k) for the Gynecare TVT, the predicate for TVT EXACT, Ethicon submitted clinical evidence supporting the safety and effectiveness of transvaginal tape for the treatment of SUI. These data included:¹⁸⁹

Medscand TVT device: U. Ulmsten, et al., An Ambulatory Surgical Procedure Under Local Anesthesia for Treatment of Female Urinary Incontinence. Non-randomized, prospective. 75 subjects, 2 year follow up.

Medscand TVT device: M. Erikson, Scandinavian Multicenter Study of the Tension Free Vaginal Tape Procedure. Non-randomized, prospective, multi-center. May 1997, 131 subjects, 1 year follow up.

¹⁸⁷ Id. pages 576:23-577:5.

¹⁸⁸ Search on 1/6/16.

¹⁸⁹ ETH.MESH.00371551.

Wang, A.C. and Lo, T.S., Tension-Free Vaginal Tape for Urinary Stress Incontinence. July 1997, 83 subjects, 3-12 month follow up.

Blaivas, J.G. and Romanzi, L., Pubovaginal Fascial Sling for Type 1 & 2 Stress Incontinence. 1996, 28 subjects, 1-6 year follow up.

Leach G.E. et al Female Stress Urinary Incontinence Clinical Guidelines. Review of 284 clinical articles comparing techniques. Sling procedure patient number is 473 with follow up of greater than 48 months.

The Institute of Medicine's report Medical Devices and the Public Health: The FDA 510(k) Clearance Process at 35 Years assesses the 510(k) process and provides recommendations to FDA.¹⁹⁰ The report on page 107 refers to a GAO study which identified that only 15% of 510(k)s submitted during FY2005-2007 include clinical data. The IOM and GAO did not evaluate or make a recommendation regarding the type or quality of clinical data used to support 510(k) devices.

It is evident from the IOM report that clinical data is not often required in a 510(k). One reason is that the new device can rely on the clinical experience with similar devices. Clinical data is needed when there is a clinical issue that cannot be answered by prior clinical evidence, engineering data or simulations. Clinical data is needed for a premarket approval application by law but also due to the fact that there are no prior devices similar enough to enable the use of prior clinical experience.

In my experience, when a 510(k) includes clinical data, the number of subjects enrolled in the supporting clinical studies and the post-treatment follow up is often similar to the clinical data supporting the Gynecare TVT that I reference above.

The 510(k) for the Gynecare TVT was cleared in 1998. FDA completed 40 PMAs in 1998 and 36 in 1999.¹⁹¹ I examined original premarket approval summaries on FDA's web site¹⁹² for 1998/1999, to identify the subjects enrolled in the clinical studies for each PMA and the duration of subject follow up. My simple hypothesis was that the Gynecare TVT study enrollment and follow up was similar to contemporaneously approved PMA devices.

In this cohort of PMAs there were several submissions for implants, some of which had clinical study enrollment in the range of 31 to 200 plus subjects and post-treatment follow up varying between a few weeks to 6, 12 or 24 months.¹⁹³ The PMA clinical study for a bulking agent used for the treatment of SUI had 178 subjects enrolled in the treatment

¹⁹⁰ IOM Report, <http://www.iom.edu/Reports/2011/Medical-Devices-and-the-Publics-Health-The-FDA-510k-Clearance-Process-at-35-Years.aspx>.

¹⁹¹ ODE Annual Report, <http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm199014.pdf>.

¹⁹² FDA PMA database, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>.

¹⁹³ Examples: P990033, P990002, P990004, P970015, P980052

group, and 177 control subjects with a 12-month follow up.¹⁹⁴

The enrollment and follow up clinical study parameters for the above PMA approved devices are not extraordinarily different than the same parameters in the clinical evidence in the 510(k) for the TVT System.

In sum, the clinical evidence submitted in the TVT 510(k) was more than 85% of 510(k)s submitted in 2005-2007 and the data was commensurate with PMA clinical data at that time.

11. In regard to the design and testing of the Gynecare TVT device and the TVT EXACT, the FDA's evaluation of substantial equivalence in a 510(k) includes an analysis of the safety and effectiveness of the device.

In August 2010, an FDA 510(k) Working Group carefully assessed the 510(k) program and provided recommendations to senior FDA management.¹⁹⁵ The report states the following in regard to safety and effectiveness determinations in 510(k)s (emphasis added):

"With the exception of certain lower risk devices that are exempt from premarket review, CDRH reviews the safety and effectiveness of medical devices for their intended use prior to marketing. Under the premarket approval (PMA) process, each manufacturer must independently demonstrate reasonable assurance of the safety and effectiveness of its device for its intended use. Under the premarket notification (510(k)) process, CDRH will clear a new device if it finds, through review of a 510(k) submission, that the device is substantially equivalent to a predicate. Generally, predicate devices, as largely class II devices, are those for which there is a reasonable assurance of safety and effectiveness with general and applicable special controls."

"The 510(k) program, as it currently exists, is intended to support FDA's public health mission by meeting two important goals: making available to consumers devices that are safe and effective, and fostering innovation in the medical device industry."

"When a predicate has a well established risk/benefit profile and is generally well regarded by the healthcare community, a premarket comparison of a new device to that predicate, with sufficient information, can provide reasonable assurance that the device, subject to general and applicable special controls, is safe and effective for its intended use."

¹⁹⁴ P980053.

¹⁹⁵ CDRH Internal Preliminary Evaluations – Volume 1, 510(k) Working Group, Preliminary Report and Recommendations, <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM220784.pdf>.

The determination of safety and effectiveness in both a PMA and a 510(k) is based on the statutory and regulatory standard of valid scientific evidence, as stated in regulations as follows (emphasis added):¹⁹⁶

"(1) Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective. After considering the nature of the device and the rules in this section, the Commissioner will determine whether the evidence submitted or otherwise available to the Commissioner is valid scientific evidence for the purpose of determining the safety or effectiveness of a particular device and whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use.

(2) Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use."

The Act has been amended several times.¹⁹⁷ One such change was the Medical Device User Fee Act of 2002 (MDUFA).¹⁹⁸ According to FDA, MDUFA was enacted "in order to provide the Food and Drug Administration (FDA) with the resources necessary to better review medical devices, to enact needed regulatory reforms so that medical device manufacturers can bring their safe and effective devices to the American people at an earlier time..."¹⁹⁹

A draft guidance issued by FDA on the determination of substantial equivalence notes the following (emphasis added): "Because devices are classified according to the level of regulatory control necessary to

¹⁹⁶ 21 CFR §860.7(c)(1).

¹⁹⁷ Amendments to the Federal Food, Drug and Cosmetic Act, <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentstotheFDCA/default.htm>.

¹⁹⁸ PL 107-250 (Oct. 26, 2002).

¹⁹⁹ MDUFA, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFA/ucm109149.htm>.

provide a reasonable assurance of safety and effectiveness, classification of a new device through the 510(k) process requires FDA to determine the issues of safety and effectiveness presented by the new device, and the regulatory controls necessary to address those issues."²⁰⁰

The guidance goes on to state "The 510(k) review standard (substantial equivalence of a new device to a legally marketed (predicate device) differs from the PMA review standard (reasonable assurance of safety and effectiveness) in that the 510(k) review standard is comparative whereas the PMA standard relies on an independent demonstration of safety and effectiveness. Nonetheless, the principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review."

12. It is my opinion the FDA October 2008 Public Health Notice and 2013 updated FDA PHN for health care workers and patients on treatment of SUI support Ethicon's position that the patient brochures were intended as only part of the interaction between the physician and patient regarding the potential treatment options for SUI and the warnings, precautions, and adverse effects for each option. It was reasonable and proper and consistent with industry standards for Ethicon to view its brochures as supplemental to physician interaction.

Manufacturers may provide patient brochures as part of the labeling for their devices. FDA can require patient brochures for a Class II device, as a special control. There is currently no such requirement for TVT devices.

A patient brochure is not intended as a comprehensive and stand-alone expression of all risks and benefits of a device. It is information to be provided to the patient to assist in the communication between a patient and her doctor.

The government describes informed consent as follows:²⁰¹

It is very important to realize that courts have increasingly held that informed consent is **a process**, not just a piece of paper.

The government describes the consent process, based on ethical principles, as follows:²⁰²

You have the right to help decide what medical care is best for you. By law, your health care providers must explain your health condition and treatment choices to you.

²⁰⁰ Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)], <http://www.fda.gov/downloads/MedicalDevices/.../UCM284443.pdf>.

²⁰¹ <http://www.ihs.gov/riskmanagement/index.cfm?module=part06>.

²⁰² Informed Consent, <http://www.nlm.nih.gov/medlineplus/ency/patientinstructions/000445.htm>.

Informed consent means:

- You are informed: you have received information about your health condition and treatment options.
- You understand your health condition and treatment options.
- You are able to decide what health care treatment you want to receive and give your consent to receive it.

To obtain your informed consent, your health care provider may talk with you about the treatment. Then you will read a description of it and sign a form. This is written informed consent.

Or, your health care provider may explain a treatment to you. They will ask if you agree to have the treatment. Not all medical treatments require written informed consent.

The testimony of Ethicon Medical Directors and others describe the role the patient brochures play in the informed consent process between the patient and her doctor. Dr. Charlotte Owens, a Medical Director at Ethicon, testified regarding patient labeling:²⁰³

"I think that one of the main things we have to do when we're speaking directly to patients, because they're — we're delivering products that come through physicians, is there's a lot of information to encourage them to have a conversation about this with their physician...you can convey general statements that initiate a conversation between the patient and their doctor to determine what's the best step."

Susan Lin, a regulatory manager at Ethicon, testified:²⁰⁴

"So it is the doctor's responsibility to communicate the risk to the patient before implant[ing] this device."

Dr. Piet Hinoul, a Medical Director at Ethicon testified:²⁰⁵

"We make patient brochures available to facilitate the conversation between her and her doctor to come up with the right decision for her treatment."

The FDA October 2008 PHN described in this report supports Ethicon's belief is that the patient brochure is not the total sum and substance of informed consent. The PHNs clearly describe FDA's expectation that doctors provide the patient a written copy of the manufacturer's labeling and discuss options and risks with the devices and techniques. The 2013 FDA web information on SUI notes that physicians should provide the patient the patient brochure or labeling, if available, and make sure the patient understands the risks and complications.

In these pronouncements FDA does not say the brochure labeling stands on its own as the sole source of information to the patient. Patient labeling is only one element of a process described by FDA. The doctor is the key intermediary and source of information between the patient and use of a device.

²⁰³ Charlotte Owens deposition, June 20, 2013, Page 341:1-10.

²⁰⁴ Susan Lin deposition, August 1, 2013, Page 1051:2-4.

²⁰⁵ Piet Hinoul, MD. PhD, deposition, June 27, 2013, Page 407:3-6.

Although manufacturers of transvaginal slings are not required to provide patient brochures it was reasonable and proper as an industry standard and practice for Ethicon to do so voluntarily for its transvaginal slings. Industry standards direct that brochures provide introductory information to the patient who then receives complete information from her doctor during the consent process. FDA's PHN's aid the patient in making communication with her doctor more informative.

13. It is my opinion there are no regulatory requirements regarding the patient brochures including the TVT EXACT brochure. The brochure is not false or misleading. The brochure is consistent with industry standards and practices.

The medical device labeling regulation, 21 CFR Part 801, does not contain any requirement for patient labeling for a prescription medical device or requirements concerning the content of patient labeling. A manufacturer may voluntarily choose to provide patient labeling in consideration of industry practice for similar devices.²⁰⁶

Patient labeling for prescription devices, e.g., brochures or videos, if provided, are subject to the misbranding provisions of the act. Also, if patient labeling is provided then 21 CFR §801.109(d) of the device prescription labeling regulation may be interpreted to include the need for attachment of an IFU to patient labeling. FDA has not enforced this provision. It is a common industry practice to attach an IFU to patient labeling.

FDA has published guidance concerning device patient labeling but FDA guidance is voluntary for manufacturers and statements in guidance are recommendations or suggestions unless what is stated is a regulatory requirement.²⁰⁷ The FDA device patient labeling guidance notes *"This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations."*

Patient labeling may describe risks and benefits of the device. The concept of "fair balance" between risks and benefits statements in labeling is a consideration for manufacturers. FDA is not prescriptive on this issue for medical devices. There is no medical device statutory or regulatory provision concerning "fair balance" in prescription or over-the-counter device labeling or advertising.²⁰⁸ There is such a provision in drug regulations but it is unenforceable for devices.²⁰⁹

²⁰⁶ A PMA approval may require labeling as a condition of approval, or a regulation may require patient labeling for a specific device. Neither of these apply to TVT devices.

²⁰⁷ Guidance on Medical Device Patient Labeling, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Documents/ucm070782.htm>.

²⁰⁸ There are advertising provisions for restricted devices in 502(q) and (r) of the act but TVT-O and TVT Abbrevio are not a restricted devices.

²⁰⁹ 21 CFR Part 202, Prescription Drug Advertising.

Given the above regulatory and best practice considerations I have examined the TVT EXACT patient brochure listed in Table 1.

TABLE 1 Patient Brochure For TVT EXACT

Brochure	Bates	IFU Attached	Information Included (examples)
TVTs including TVT EXACT	ETH.MESH.08003295-08003302	yes	Ditto

In general, in the patient brochure the patient is advised to talk to her doctor about her condition, the treatment options, and the risks and benefits. This is consistent with the 2008 and 2013 FDA Public Health Notice instructions regarding communication between doctors and patients on treatment of SUI, as detailed in Section IV of this report.²¹⁰

The risk section of the brochure accurately states that all surgical procedures present risks. Risks are listed and the patient is referred to the IFU information for a complete description of risks. The patient is informed to talk with her doctor about the risks. Again, this communication between doctor and patient is consistent with the FDA PHN instructions to doctors and patients concerning treatment of SUI.

The potential or claimed benefits of TVT EXACT are discussed in the brochure.

There are bases for the claims in the patient brochures. The claim of reduced operative time is reasonable when compared to the operative time for open surgical procedures and that sling procedures are generally out patient procedures as noted by FDA. The claims of long-term safety and effectiveness are supported by clinical data, testimony, and by professional organization opinions detailed in this report.

Ethicon patient brochures state, for example, "my doctor explained there is a minimally-invasive, simple treatment called TVT."²¹¹ FDA statements to its Advisory Panel and by professional organizations in Sections IV and V of this report, and deposition testimony, support Ethicon's claim of TVT's minimal invasiveness.

TVT Classic, the predicate for TVT-EXACT, is within a group of products designated by FDA as 1st generation slings. In the September 9, 2010 presentation to the Obstetrics and Gynecology Devices Panel, FDA describes the 1st generation suburethral slings as "minimally-invasive."²¹²

The AUGS statement I describe in Section V of this report states "Developed in the early 1990's, midurethral slings (MUS) treat stress

²¹⁰ See reference to other TVT brochures in II.F.5. of this report.

²¹¹ ETH.MESH.01613143-46.

²¹²

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM272113.pdf>, pages 45 and 47.

urinary incontinence (SUI) in a minimally invasive, generally outpatient procedure."

Dr. Martin Weisberg describes TVT and its minimal invasiveness in the following testimony:

"Do you believe that the term "minimally invasive" is an accurate way to describe Gynecare TVT-O?

THE WITNESS: Yes. It was similar (to TVT Classic or retropubic) in that there were two skin incisions and one urethral incision."²¹³

The brochure is compliant with the device labeling regulations and there is no basis to find it false or misleading.

The brochure is also consistent with industry standards and practices. The brochure contains the important recommendation for the patient to speak with her doctor about her treatment options and best course of action. The brochures reasonably include risks and benefits information that can be expanded upon in the communication between the patient and her doctor.

14. It is my opinion that there is no evidence that the TVT Classic or TVT EXACT devices were inadequately manufactured or that they failed to meet specifications.

There is no testimony or litigation production evidence I have received and reviewed attesting to a manufacturing nonconformity of the TVT Classic or TVT EXACT related to a Plaintiff's condition.²¹⁴

I requested and was provided by counsel a record of recalls for the TVT devices. There was one recall in 2000 for the TVT Classic due to needle pull off from the tape.²¹⁵ In any case, in my opinion the physician can visually detect this type of malfunction during surgery.

My review of the FDA Warning Letter database on January 29, 2016 revealed no Warning Letters to Ethicon related to Ethicon TVT devices.²¹⁶ FDA may issue a Warning letters to a manufacturer if it determines, typically based on inspection observations, that there are violations of FDA law and regulations.

My review of TVT EXACT Issue Reports (See opinion 9) include product related complaints that meet the FDA definition of malfunctions. According to Ethicon complaint procedures (See opinion 5) Ethicon must investigate these events and trend events. Complaint trends may identify manufacturing nonconformities that require corrective and preventive action. I did not identify any records of CAPAs for TVT Abbrevio related to manufacturing defects in the time period associated with this litigation.

²¹³ Weisberg deposition, 8/9/13, Page 985:2-8.

²¹⁴ A nonconformity is the nonfulfillment of a specified requirement per 21 CFR §820.3(q).

²¹⁵ ETH.MESH.00108420-00108423.

²¹⁶ FDA Warning Letter database, <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters>.

15. It is my opinion that Ethicon substantially complied with FDA premarket and related quality system requirements and industry standards and practices prior to marketing TVT EXACT; clinical information continues to support the safety and effectiveness of TVT EXACT.

I examined whether (1) ETHICON conducted adequate testing according to regulations and industry standards supported clearance of TVT EXACT and continued marketing of the device, and (2) whether TVT EXACT was ever found unsafe or ineffective. I can set aside (2) by stating the simple answer that FDA has never found TVT EXACT to be in violation of the laws and regulations it administers including violation of adulteration and misbranding prohibitions.

The TVT EXACT 510(k) submissions meet FDA requirements, industry standards and best practices

In general, regulations require a new device to be cleared or approved by FDA, unless otherwise exempt from such requirements, before it can be marketed.²¹⁷ The TVT EXACT device was submitted as a Special 510(k). According to FDA, the Special 510(k) relies on manufacturer compliance with the design control requirements of the Quality System Regulation (21 CFR Part 820). A Special 510(k) and may be submitted for a modification to a manufacturer's own device that has been previously cleared under the 510(k) process. The TVT EXACT was a modification of the cleared Ethicon TVT Classic.²¹⁸

A Special 510(k) allows the manufacturer to declare conformance to design controls and requires only a summary of the testing, not the full reports of the data.²¹⁹

I analyzed the TVT EXACT Special 510(k) for the information a manufacturer must submit to FDA.²²⁰ The Special 510(k) includes the following information:²²¹

²¹⁷ 21 CFR §807.81 and 21 CFR §814.1.

²¹⁸ ETH.MESH.00020245-00020246.

²¹⁹ How to Prepare a Special 510(k), <http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket submissions/premarketnotification510k/ucm134573.htm>.

²²⁰ How to Prepare a Special 510(k), <http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket submissions/premarketnotification510k/ucm134573.htm>.

²²¹ ETH.MESH.00020232.

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Attachment 1 Special 510(k) Decision Paradigm

The information meets the regulatory requirements for a Special 510(k). The content of the TVT EXACT Special 510(k) follows the form and content as recommended by FDA in its Special 510(k) guidance and is consistent with industry standards and practices. Pages 54-57 of the 510(k) list the appropriate premarket verification tests conducted by Ethicon, the success criteria for the tests and the results.²²² I conclude from this information after analysis of the data against FDA's criteria for equivalence that TVT EXACT is equivalent to TVT Classic and the accessories are equivalent, based on intended use, descriptive characteristics vis-a-vis that of the predicates, and test data.

Ethicon submitted a Special 510(k) in 2013 for a modification to TVT EXACT.²²³ The changes were described as follows:

The following changes are proposed for the GYNECARE TVT EXACT™:

- o A new performance requirement - Trocar Assembly Lateral Tip Bending Strength will be added to the device design requirement of the device;
- o In order to ensure that the GYNECARE TVT EXACT™ meets the above design requirement, the geometries of Trocar Shaft tip and Trocar Sheath inner tip will be changed.
- o The Package Insert for the device will be updated accordingly.

Appropriate design control data and information were provided on pages 34-37 of the submission consisting of a risk assessment and design verification data as recommended in FDA guidance for Special 510(k)s. I assessed the submitted information and found it meets the requirements for a Special 510(k).

Supportive evidence of the safety and effectiveness of TVT EXACT

²²² ETH.MESH.00020284-00020287.

²²³ ETH.MESH.21535530-21535608.

Ethicon Clinical Expert Report provide evidence of the safety and effectiveness of TVT EXACT.

The May 28, 2010 Gynecare TVT EXACT Clinical Expert Report by Dr. Aaron Kirkemo, a medical director at Ethicon, compares the TVT EXACT to TVT Classic as follows:²²⁴

Both systems use the same laser cut polypropylene mesh implant as the laser cut GYNECARE Tension-free Vaginal Tape (TVT) System. Both implant sleeves are the same design and material. Save for the means of attaching the implant/implant sheath and the trocar sheath to the trocar shaft (EXACT) versus implant/implant sheath and trocar needle to the trocar handle the IFU's are identical. EXACT requires one less cystoscopy. The needle tip radiuses are identical as are the curvature of the trocar sheath/trocar compared to the Classic TVT needle. The TVT EXACT trocar sheath is 4.2 mm versus 5.0 mm for the TVT "Classic" device. Hence it was felt that review of the "Classic" GYNECARE Tension-free Vaginal Tape (TVT) System safety and efficacy data would be sufficient to assess the value of the new system relative to competitive retropubic devices as well as for the alternative surgical approaches for management of SUI.

The CER includes an extensive literature review of midurethral slings and a review of complaint data. The literature review concludes:

The above data are sufficient to demonstrate compliance with the essential requirements covering safety and performance of the GYNECARE TVT EXACT™ Continnence System under normal conditions of use. No additional clinical data is required.

A July 16, 2013 CER by Dr. Piet Hinoul, a medical director at Ethicon, again analyzes the literature and complaint data and updates the safety and performance of Ethicon TVT devices including the TVT EXACT.²²⁵ The CER notes the following which undoubtedly led to the second Special 510(k):

During 2012 it was however noted that there had been an upward trend of TVT EXACT complaints for trocar sheath tip bending/cracking during use. No root cause for this could be established. The incidence (0.09%) this is within the estimated occurrence rate for faillure modes that could lead to bent/cracked trocar sheath tips of 0.1% as per the product's FMEAs. There were no patient harms associated with this complaint.

The CER concludes the following:

²²⁴ ETH.MESH.01269170-01269207.

²²⁵ ETH.MESH.10683482-10683816.

The literature review data, taken together with previously available clinical and pre-clinical data, are sufficient to demonstrate State of Art compliance with the essential requirements covering safety and performance of the GYNECARE TVT™ Family of products under normal conditions of use. No additional clinical data is required. No previously unidentified harms or hazards were identified in this review.

No information was provided from either the literature or PMS data to indicate that any new performance issues are occurring in the clinical setting that were previously unknown.

After manual review and analysis, no new hazards, increased risk or unexpected adverse events were noted. The clinical evidence provides support that GYNECARE TVT™ meets the Essential Requirements of the Medical Device Directive 2007/47/EC.

Expert Opinions Conclude TVTs, Including TVT EXACT, continue to Be Safe and Effective

The findings by FDA and its advisory panel in 2011, the position statements of clinical professional associations and a clinical standard organization I detail in this report attest to the continued safety and effectiveness of TVT EXACT.

16. It is my opinion that the safety and effectiveness of laser cut mesh was properly verified according to regulations. Mechanically cut mesh continued to be reasonably safe and effective. Ethicon's addition of laser cut mesh was reasonable and proper and consistent with industry standards.

The FDA quality system regulation, 21 CFR Part 820, requires that design changes to a device must be validated or where appropriate verified, reviewed, and approved before their implementation.

Ethicon produced TVT EXACT with a laser cut edge.²²⁶ The mechanically cut edge was distributed first by Ethicon. Ethicon conducted Voice of Customer (VOC) interactions with doctors to learn of their views on laser cut mesh prior to its introduction.²²⁷

An Ethicon presentation in January 2005 reported that laser cut and mechanically cut mesh have the same physical attributes in regard to elongation, uniaxial tension, flexural modulus and pull-out force but structural integrity is different. The presentation describes a 2 week animal study where the two types of meshes maintained equal histological and mechanical properties.²²⁸

There are several verification tests reports verifying the safety and effectiveness of laser cut slings. Ethicon test reports compare the

²²⁶ ETH.MESH.10683488.

²²⁷ ETH.MESH.06878438-306878439.

²²⁸ ETH.MESH.00442129.

elongation, particle loss and rigidity of both meshes.²²⁹ There are design verifications of laser cut mesh sheath removal.²³⁰ A biocompatibility report states "This base material is intrinsically safe and without significant effects...This, the clinical use of laser-cut GYNECARE TVT PROLENE mesh implant is not expected to result in any adverse biocompatibility effects for patients."²³¹ Ethicon conducted a particle loss with a test report dated 3/9/06.²³²

A risk management report of TVT laser cut mesh assessed the potential harms, their severity and estimated frequency, and determined that a risk benefit analysis was not needed.²³³ Ethicon assessed complaints for laser cut mesh to support the laser cut mesh risk management plan.²³⁴

There are three clinical expert reports pertaining to laser cut mesh. The first dated 2/28/06 by Drs. Weisberg and Robinson is for TVT Secur and concludes, "It is not anticipated that there will be any clinical differences in the devices that utilize laser cut mesh."²³⁵ The second dated 3/7/06 is for TVT Classic, TVT-O and TVT-A concludes "The physical properties that might affect clinical performance are essentially the same...Clinical data is not necessary to establish the safety and effectiveness of the devices affected by these changes."²³⁶ The third report dated 4/18/06 applies to the same devices.²³⁷

Ethicon documented a change notice for laser cut mesh indicating the completion of a new design matrix and the need for new quality plan and device master record. The change notice concludes that a new submission to FDA is not needed.

Ethicon continued to market mechanical and laser cut mesh to meet customer preferences.

Ethicon verified the laser cut mesh as evidenced by the tests and analyses noted above. These tests and analyses and the changes indicated on the change notice are consistent with industry standards and practices.

Expert Reports for Plaintiffs

I reserve the right to more specifically address the opinions of Drs. Pence and Parisian as I have set out previously and to amend my opinions pending further discovery.

²²⁹ ETH.MESH.01320328-33, 021614610-24 and 06696367-79.

²³⁰ ETH.MESH.00309290-301 and 00309314-31.

²³¹ ETH.MESH.04939001.

²³² ETH.MESH.00309332-50.

²³³ ETH.MESH.00223779-84.

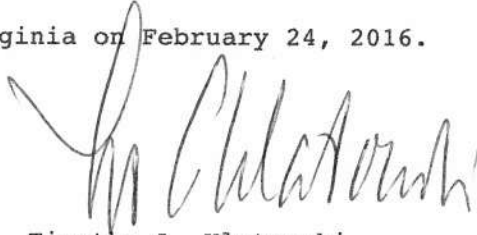
²³⁴ ETH.MESH.01784779-82.

²³⁵ ETH.MESH.01189423-39.

²³⁶ ETH.MESH.01784823-28.

²³⁷ ETH.MESH.00309275-78.

Executed in Herndon, Virginia on February 24, 2016.

A handwritten signature in black ink, appearing to read "Timothy A. Ulatowski". The signature is fluid and cursive, with the first name being the most prominent.

Timothy A. Ulatowski

APPENDIX A
CV for Timothy A. Ulatowski

CV

Timothy A. Ulatowski

Regulatory Consultant/Medical Devices

Extensive Regulatory Experience ~ Risk Management ~ Technical Expert

A unique medical device consultant with extensive experience in both premarket evaluation of new medical devices and enforcement of FDA laws and regulations. Over 40 years of significant public health achievements, creating major regulatory programs and policies, developing and implementing strategic and risk management plans, and building collaborations with global regulatory partners and industry. Proven skills in advising industry on regulatory issues, assessing compliance and enforcement actions, evaluating premarket documents, managing and supervising large organizations, resolving complex technical and scientific problems of individual firms to those of national and international scope, and communicating to diverse audiences.

Selection of Notable Accomplishments

Technical leadership on numerous compliance, enforcement and recall actions, many of national or global importance

Initiated use of novel corporate enforcement actions

Created effective internal quality management system used as a model program in FDA

Lead author of international guidance documents on aspects of the Global Harmonization Task Force medical device regulatory model adopted by many countries

Recognized in "Top 100" of medical device professionals/MDDI

Primary FDA reviewer of hundreds of Premarket Notifications, Investigational Device Exemptions, Premarket Approval Applications, recalls and compliance actions

Leader of team that developed the current FDA device standards program

Author of many key FDA premarket guidance documents, technical standards and publications

Senior advisor to DOJ and FDA criminal investigations office

Lead for agency on many GAO, OMB and Congressional activities

FDA spokesperson to major press and to large audiences

HHS Team Leader and technical expert remediating Anthrax contamination of Senate and Postal Service buildings

Creator of FDA/CDC/EPA tripartite collaborations on chemical germicides and co-author of current FDA/EPA national regulatory scheme for chemical germicides

Co-author and collaborator on sharps injury prevention guidance, related OSHA and NIOSH regulations and policies, resulting in documented reduction of injuries

Recipient of numerous major FDA awards

Expert witness for Defendants and Plaintiffs in numerous litigations; deposition and court testimony

Expert trainer on behalf of FDA and US Dept of Commerce for foreign regulatory staff and FDA staff

Successful, numerous premarket, postmarket and compliance accomplishments for large and small manufacturer or entrepreneur clients

Professional Experience

Regulatory Consultant, Medical Devices

April 2014 - Present

- Regulatory consulting support to the medical device industry in areas of premarket, postmarket, compliance, and combination products
- Expert witness in litigation

NSF Health Sciences (formerly Becker & Associates Consulting Inc.): Vice President, Regulatory and Compliance

June 2012 – April 2014

- Ensured effective and timely solutions to a variety of FDA regulatory and legal issues
- Provided expert advice and recommendations on premarket, quality systems, compliance and device reporting
- Trained industry staff, international regulators and FDA staff on FDA medical device regulations and procedures
- Served as expert witness in litigation

NDA Partners LLC: Principal

January 2011 – June 2012

- Advised clients on FDA regulations and law regarding product submissions, compliance and enforcement actions, and postmarket surveillance activities
- Served as an expert witness in litigation
- Conducted due diligence

FDA, CDRH: Director, Office of Compliance and Senior Advisor for Enforcement

January 2003 – January 2011

- Managed and supervised office of four divisions and 180 professional staff responsible for ensuring compliance with medical device laws and regulations
- Directed FDA device quality system and bioresearch enforcement programs
- Directed inspection assignments and assessed quality system and bioresearch monitoring inspection reports and company/investigator/sponsor/IRB responses to determine violations
- Worked with all FDA districts, ORA and drug, biologics and food compliance executives to formulate enforcement strategies and actions

- Hands on evaluation and management of recalls, device advertising and promotion, MDRs, registration and listing, and medical device field resource allocation and prioritization
- Created new device enforcement policies and programs, directed implementation of the Commissioner's strategic action items, and participated in executive strategic planning at the agency and center levels
- Co-leader of FDA Medical Device Field Committee, an ORA/CDRH collaboration
- Initiated comprehensive training program for compliance staff and web-based information for the public
- Co-leader of 2010 user fee legislation post market committee, devising proposals and strategies with key Center and Agency staff for next round of legislation
- Senior Device Enforcement Advisor September 2010 – January 2011

FDA, CDRH: Head of USA Delegation, Global Harmonization Task Force and FDA representative to GHTF Study Group 1 Premarket

January 1995 - October 2010

- Managed the activities of the USA FDA participants to the GHTF Steering Committee and the five study groups; collaborated with USA industry task force members, USA leader on the GHTF Steering Committee for last four years
- Coordinated creation and review of documents and recommended agency decisions on pending documents to Center Director
- Primary author of several GHTF documents, including the original premarket "STED" document, and Global Model document, which are now used internationally
- Frequently trained international government staff on GHTF and FDA procedures

FDA, CDRH/Office of Device Evaluation: Director, Division of Dental, Anesthesiology, General Hospital, and Infection Control Devices

December 1996 – January 2003

- Managed premarket activities, such as review of premarket submissions and investigational applications, panel meetings, guidance development, and collaborative support for other CDRH offices
- Led development of the division during a major reorganization
- FDA lead on numerous international standards committees, reengineering task groups, and interagency task forces dealing with significant public health issues
- Succeeded in reducing review times while improving the quality and rigor of reviews
- Primary reviewer on numerous 510(k)s, IDEs, and PMAs
- Agency and ISO technical expert on medical device sterilization and disinfection

Prior FDA experience, short summary

Device Evaluation Associate Director, Branch Chief and front line 510(k), IDE, and PMA reviewer

Director, Investigational Device Staff, IDE application review and protocol advice

New Drug Evaluation Product Manager, NDA and IND review and advisory committee exec sec

Microbiologist, National Center for Antibiotic Analysis, drug assessments

Prior to college and FDA career: US Army 1968 – 1971

Education

- Master of Science/Physiology with Biomedical Engineering emphasis, 1988 GPA 4.0

Georgetown University School of Medicine

- Bachelor of Science/Microbiology, 1974 cum laude

Pennsylvania State University

- Food and Drug Law, George Washington University School of Law, 1978
- Computer Science, University of Maryland and Charles County Community College, 2000-2005
- Numerous FDA sponsored or supported courses, for example, in risk management, quality systems, clinical studies, human factors, statistics, sterilization engineering

APPENDIX B

Materials Reviewed and Public Sources of References

Public Sources of References to Food and Drug Laws, FDA Regulations, FDA Guidance, FDA Policy and Procedures, and Definitions

Federal Food, Drug, and Cosmetic Act:

<http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdact/default.htm>

21 Code of Federal Regulations:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>

FDA Guidance and Policies: www.fda.gov

Merriam-Webster Online Dictionary

Global Harmonization Task Force web site, www.ghtf.org

APPENDIX C PRIOR TESTIMONY

University of Pittsburgh of the Commonwealth System of Higher Education
d/b/a University of Pittsburgh v. Varian Medical Systems, Inc.

Civil Action No.: 2:08-cv-01307 (USDC, Western District of
Pennsylvania)

David M. Kloss, et al, v. I-Flow Corporation, et al, Case No. 2:10-cv-
00295-JFC (USDC, Western District of Pennsylvania)

Retractable Technologies, Inc. and Thomas Shaw v. Becton, Dickinson and
Company, Civil Action No.2:08-cv-16 (Folsom) (USDC, Eastern District of
Texas Marshall Division)

Diagnostic Devices Inc, v. Pharma Supply, Inc. et al, Diagnostic
Devices Inc, v. Taidoc Technology Corporation, Case No.3:08-CV-00149-
MOC-DCK (USDC, Western District of North Carolina, Charlotte Division)

Brenda F. Kitrosser v. Nuvasive, Inc. et al., Case No: 37-2009-
00099700-CU-MM-CTL [Consolidated with Case No: 37-2010-00099400-CU-PO-
CTL] (Superior Court of the State of California In and For the County
of San Diego, Central Branch)

Superior Court of New Jersey, Law Division, Atlantic County

In re Pelvic Mesh/ Gynecare Litigation, Case No.291 CT, Master Case
6341-10

Jackson, et al v DePuy Orthopedics, No. CAL 10-32147 (Prince George's
County, MD)

Strum v. DePuy Orthopaedics, Inc., et al., No. 11 L 009352 (Circuit
Court, Cook County, Illinois)

Dorney-Madgitz v. DePuy Orthopedics, Inc., et al., 5:11-cv-001240-RBS
(USDC, Eastern District of Pennsylvania)

Weinstat, et al. v. Dentsply International, et al., San Francisco
Superior Court No. CGC-04-432370

Braun v. Medtronic Sofamor Danek, USDC, District of Utah, Central
Division, Case 2:10-cv-01283

Connie Schubert and Kevin Schubert v. Ethicon, Inc., Ethicon Women's
Health and Urology, a division of Ethicon, Inc., Gynecare, and Johnson
and Johnson, et. al., In the Circuit Court of Jasper County, Missouri
at Joplin, Case No. 10AO-CC00219

Sekisui America Corporation and Sekisui Medical Co., Ltd. v. Richard
Hart and Mary Louise Trudel-Hart, USDC, Southern District of New York,
Case 1:12-cv-03479-SAS (for Plaintiff)

Carol Lewis and Kenneth Lewis v. Ethicon, USDC, Southern District of
West Virginia, MDL No. 2327

April Christine Cabana v. Medtronic Inc. (et al), Superior Court of the
State of California, County of Los Angeles, Case No. BC 465 313

Christine Napolitano v. Synthes, Inc., USDC, District of Connecticut,
Civil Action 3:09-CV-00828

Herlihy-Paoli v. DePuy Orthopedics, Inc., et al, 3:12-CV-04975-K (USDC,
Northern District of Texas, Dallas Division)

City of Lakeland Employees Pension Plan v. Baxter International Inc.,
No. 10-cv-6016, USDC, Northern District of Illinois

Smith v. Baxano, Inc. et al, Superior Court of Washington for Snohomish
County, Case No. 13-2-02714-1

Andrea Smith v DePuy Orthopedics, et al., District Court of Tulsa
County, Oklahoma, No. CJ-2011-05804

Zimmer NexGen Knee Implant Products Liability Litigation, USDC,
Northern District of Illinois, Eastern Division, MDL No. 2272, Master
Docket No.:1:11-cv-05468

Sandra Garcia v Rodolfo J. Walss, MD, Johnson & Johnson, Inc. and Ethicon, Inc., District Court, 103rd Judicial District, Cameron County, Texas, Cause No. 2013-DCL-3511-D

Laura Ness v Depuy Orthopedics, Inc., et al., In the Circuit Court for Baltimore City, Case No. : 24-C-14-002465

Consolidated Fresenius Cases, Commonwealth of Massachusetts, Middlesex SS., Superior Court Department of the Trial Court, Civil Action No. 2013-03400-O Session

Aoki, Christopher, Greer, Klusmann, Peterson, Thibodeau (separate Plaintiffs) v DePuy Orthopedics, Inc. et al.,. USDC, Northern District of Texas, Dallas Division, MDL No. 2244

Center City Periodontists, P.C., et al. v. Dentsply International, Inc., Eastern District of Pennsylvania, Civil Action No. 10-00744.

Michael Parker, Individually and Amy Parker, Individually v. Veronica A. Vasicke, MD; Bluegrass Orthopedics & Hand Care, PSC; and I-Flow Corporation, Fayette Circuit Court, Eighth Division, Civil Action No. 12-CI-3543.

Court Testimony:

Strum v. DePuy Orthopaedics, Inc., et al., No. 11 L 009352 (Circuit Court, Cook County, Illinois)

Brenda F. Kitrosser v. Nuvasive, Inc. et al., Case No: 37-2009-00099700-CU-MM-CTL [Consolidated with Case No: 37-2010-00099400-CU-PO-CTL] (Superior Court of the State of California In and For the County of San Diego, Central Branch)

Weinstat, et al. v. Dentsply International, et al., San Francisco
Superior Court No. CGC-04-432370

Sekisui America Corporation and Sekisui Medical Co., Ltd. v. Richard
Hart and Mary Louise Trudel-Hart, USDC, Southern District of New York,
Case 1:12-cv-03479-SAS

Becky S. Anderson v. Medtronic, Inc. (et al), Superior Court for the
State of Washington, County of King, No. 12-2-17928-0 SEA

Donald Gustafson v. Zimmer, Inc., District Court, Collin County, Texas,
366th Judicial District, Cause No. 366-03111-2011

Herlihy-Paoli v. DePuy Orthopedics, Inc., et al, 3:12-CV-04975-K (USDC,
Northern District of Texas, Dallas Division)

Andrea Smith v DePuy Orthopedics, et al., District Court of Tulsa
County, Oklahoma, No. CJ-2011-05804

Alysia Ogburn-Sisneros, as personal representative of the estate of
Billy Ogburn, Sr., Plaintiff v. Fresenius Medical Care Holdings,
Inc.d/b/a Fresenius Medical Care North America, Inc, Fresenius USA,
Inc., Fresenius USA Manufacturing, Inc., Fresenius USA Marketing, Inc.,
and Fresenius USA Sales, Inc., Defendants, Commonwealth of
Massachusetts, Superior Court Department, Civil Action No. 13-5050

Center City Periodontists, P.C., et al. v. Dentsply International,
Inc., Eastern District of Pennsylvania, Civil Action No. 10-00744.